Novel Intramolecular Nucleophilic Addition Reactions: Formation of Unusual *N-O*-Heterocyclic Enones

By

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Novel Intramolecular Nucleophilic Addition Reactions:

Formation of unusual *N*-*O*-Heterocyclic Enones

Adwait R. Ranade, B. Tech.

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Cyclic enaminones, which possess vinylogous amide functionality in a closed ring structure, have been extensively studied and their versatility continues to spark interest in newer and more efficient methods for their enantiospecific synthesis and chemical modification. Due to their unique structural and chemical properties, enaminones are of interest in natural product and diversity-oriented synthesis (DOS). Many biologically active natural products and alkaloids belong to the indolizidine, pyrrolizidine, and quinolizidine classes of molecules. They can be synthesized via enaminones as intermediates. Therefore, the goal of this project was to develop a general methodology for the facile and enantiospecific synthesis of the enaminone scaffolds and then generate a library using this method.

It was hypothesized that one-pot Boc deprotection/cyclization of β-hydroxylaminoynones would render *N*-oxy enaminones, which can be easily converted to enaminones by reductive cleavage of the *N*-*O* bond. Due to complications observed with such type of chemistry, the route was modified and a one-pot TBS deprotection/cyclization of β-hydroxylaminoynones was carried out. This approach yielded novel seven-membered *N*-*O* heterocyclic compounds. The

mechanism is thought to be a 7-endo-dig cyclization to yield seven-membered 3,4-dihydro-1,2-oxazepin-5(2*H*)-ones. Reductive cleavage of the *N*-*O* bond in 3,4-dihydro-1,2-oxazepin-5(2*H*)-ones rendered 2,3-dihydropyridin-4-(1*H*)-ones (enaminones). Thus, the 7-membered novel oxazepinone scaffold and the known enaminone scaffold can be used for constructing diverse compound libraries. Additional chemical transformations can also be carried out on these scaffolds to obtain additional diverse chemotypes.

Acknowledgements

I would like to thank Professor Dr. Gunda I. Georg from bottom of my heart for her mentorship, encouragement and constant support that helped me in my graduate career.

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My thanks to all the faculty, staff and students at the University of Kansas and the University of Minnesota for a wonderful experience.

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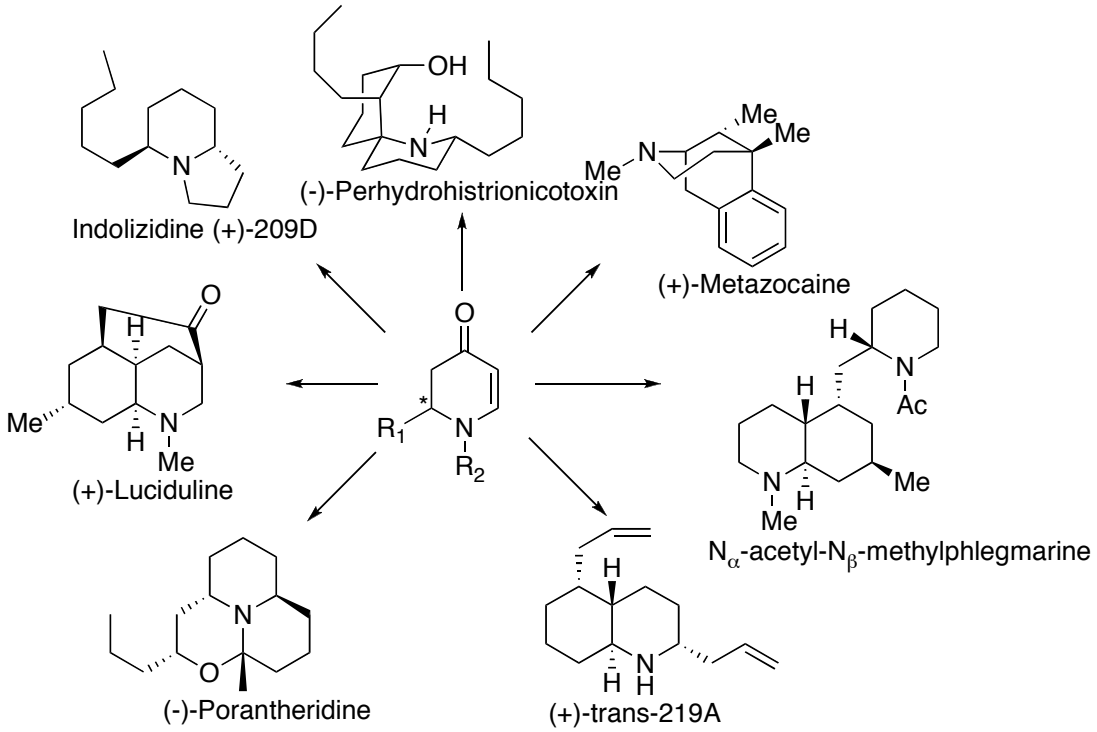
1. Background

1.1 Introduction

About 10^{60} small molecules with molecular weight less than 500 exist in the "Chemical Diversity Space." Only 10^{8} molecules have been synthesized or isolated from natural sources so far.[1] Heterocyclic compounds containing nitrogen contribute to a major portion of various classes of therapeutic agents. In many cases, these structures contain a piperidine moiety.[2,3]

Figure 1. Enaminones as Important Intermediates for Various Alkaloids



Cyclic *Z*-enaminones are a very well known class of molecules that have been extensively studied and their versatility and unique chemical properties continue to spark interest in novel and more efficient methods for their enantiospecific synthesis.[4] Enaminones are very important intermediates in the synthesis of alkaloids[10] (Figure 1).

Figure 2. Structural Differences amongst Amide, Enamine and Enaminones

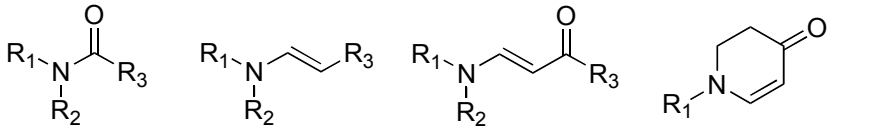
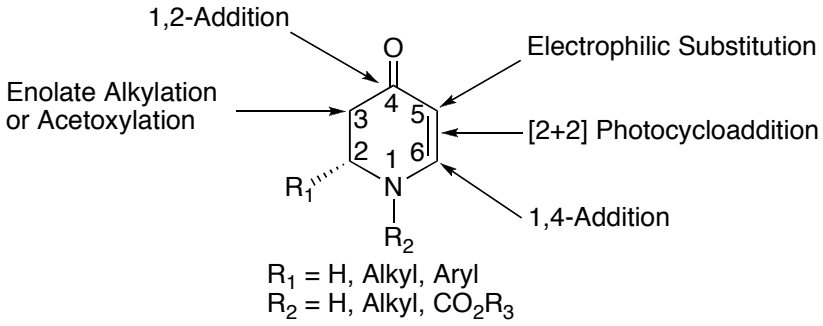


Figure 2 shows the structural differences amongst an amide, an enamine, an enaminone and a cyclic *Z*-enaminone. Enamines can be described as vinylogous amines, whereas, enaminones are vinylogous amides. Cyclic *Z*-enaminones possess the vinylogous amide functionality in a closed ring structure. Enaminones are comparatively more stable and reactive than the corresponding enamines, which are sensitive to oxidation and hydrolysis and sometimes difficult to isolate.[5] The conjugation of the enamines to a carbonyl functionality weakens their reactivity and makes them less robust than amides, but responsible for their versatile and unique properties.[6]

Figure 3. The Versatile 2,3-Dihydro-4-pyridones



A large variety of transformations are possible on this unique scaffold as shown in Figure 3.[7,10] At position 1, the nitrogen atom can carry a variety of moieties such as a proton, different alkyl groups or a carboxylate. The C-2 position bears a substituent R_1. A variety of substituents can contribute to additional diversity. Also, by changing the stereochemistry at the C-2 position, one can obtain different enantiomers. The C-3 position is acidic due to the presence of adjacent carbonyl group. Various types of substitution are possible at C-3 position via enolate alkylation or acetoxylation. A large number of transformations can be carried out on the carbonyl at C-4. Some of the examples of these transformations are 1,2-addition at C-4 using reagents such as Grignard reagents, alkyl or aryl lithium reagents, etc. The C-5 position is relatively nucleophilic, so a variety of electrophilic additions (e.g. addition of iodine) are possible on the C-5 carbon. The double bond between C-5 and C-6 can be subjected to a [2+2] photocycloaddition with dienophiles. The C-6 position can be subjected to various 1,4-addition reactions. Some of the transformations include 1,4-hydride addition by using reagents such as L-Selectride, Michael addition using copper

reagents, etc. Therefore, the unique structural and chemical properties of enaminones is of interest in natural product and diversity-oriented synthesis (DOS).[8]

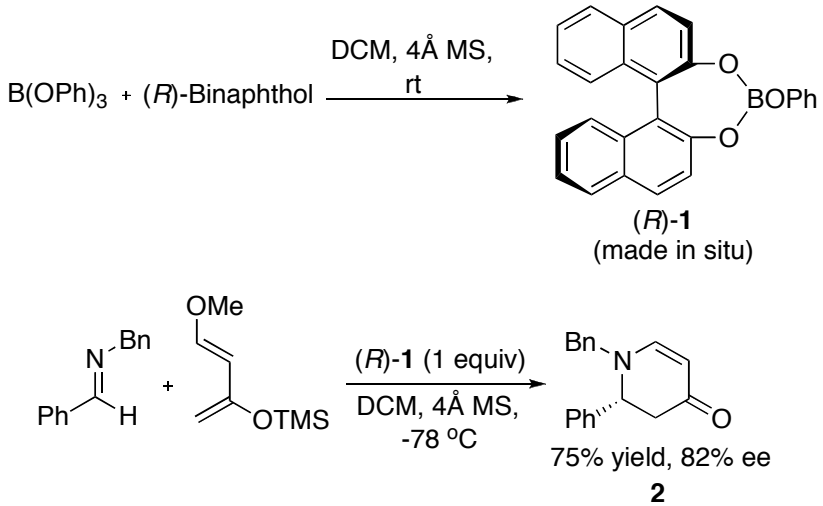
1.2 Syntheses of Enaminones

Over the last 20 years various routes for synthesizing enaminones have been established. All these methods aim to prepare the enaminones in high yields and excellent steroselectivities by employing either various chiral catalysts or using chiral non-racemic starting materials. Methods that are effective in generating these unique scaffolds are discussed below.

1.2.1 Ishihara's Strategy

In 1997, Kazuaki Ishihara et al. reported a facile synthesis of enaminones by employing the asymmetric aza Diels-Alder reaction of imines.[9]

Scheme 1. Ishihara's Approach



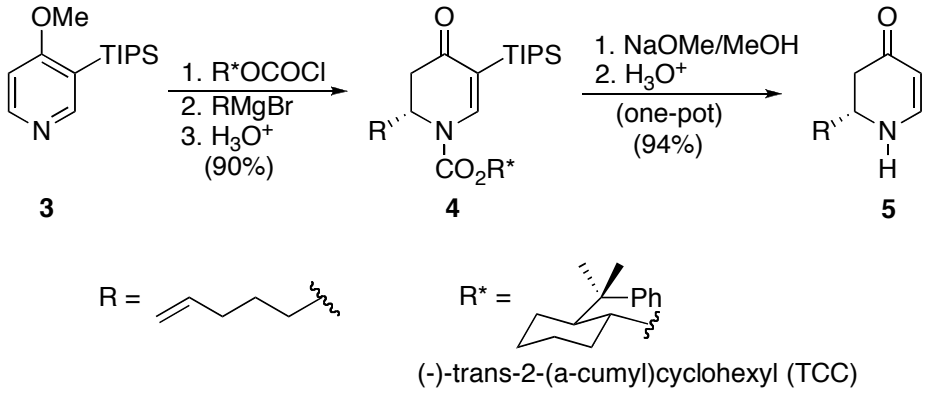
The chiral boron complex (*R*)-**1** is prepared in situ by stirring equimolar amounts of optically active (*R*)-binaphthol and triphenyl borate in dichloromethane at room temperature for 1 hour in the presence of 4Å molecular sieves. The chiral complex (*R*)-**1** thus formed in situ is used to promote the aza Diels-Alder reaction of the imine with the Danishefsky diene in the presence of 4Å molecular sieves at -78 °C for several hours. After usual workup and purification by column chromatography, the enaminone **2** is isolated in 75% yield and 82% ee. The new chiral boron reagent (*R*)-**1** offers various advantages including the following. (1) Both chiral binaphthol and phenyl borate are available commercially and the catalyst can be easily generated. (2) Isolation is not difficult and binaphthol can be recovered quantitatively. (3) Either enantiomer of the product can be synthesized since the required reagents are readily available in both *R* and *S* forms.

1.2.2 Comins' Strategy

In 1999, Daniel Comins reported a very efficient method to synthesize chiral non-racemic enaminones (Scheme 2).[10] In this method, a chiral acylpyridinium salt is prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine (**3**) and (-)-trans-2-(a-cumyl)cyclohexyl chloroformate (TCC chloroformate). This is then treated with a Grignard reagent and an aqueous workup to yield the N-protected enaminone **4** with very good diastereoselectivities (85-95%). After the major diastereomer is separated by either recrystallization or column chromatography, standard chemical

transformations are performed to remove and recover the chiral auxiliary and cleave the triisopropylsilyl group in order to get the free enaminone **5**.

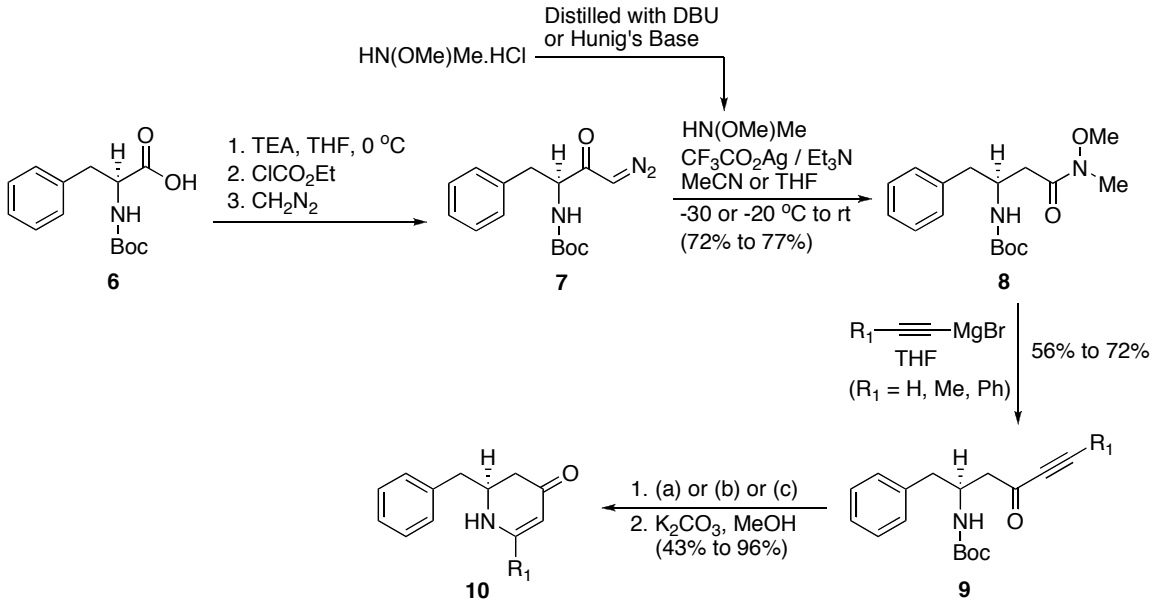
Scheme 2. Comins' Approach



1.2.3 Georg's Strategy

In 2006, the Georg group developed a novel method for the intramolecular cyclization of amino ynones to yield the enaminones (Scheme 3).[11] In this facile synthesis of enantiopure enaminones, commercially available enantiopure α-amino acids are converted into α-diazoketone by treatment with diazomethane, which is generated in situ. This is then reacted with silver triflate in the presence of triethylamine and free Weinreb amine (generated by distillation of the Weinreb salt in the presence of a base like DBU or Hunig's Base) to generate a Weinreb amide. The addition of an alkynyl Grignard reagent to the amide furnishes the ynone intermediate.

Scheme 3. Georg's Approach



The final cyclization is carried out by subjecting the ynone to either of the conditions from (a), (b) or (c). In condition (a), the ynone is treated with a solution of concentrated HCl in dioxane followed by treatment with potassium carbonate in methanol as solvent. In condition (b), the ynone is dissolved in anhydrous CH_2Cl_2 under an argon atmosphere at -78 °C and a solution of TMS-I CH_2Cl_2 is added. After allowing the reaction mixture to warm to room temperature, more TMS-I is added and then this is followed by treatment with potassium carbonate in methanol as solvent. In condition (c), the ynones are subjected to a solution of NaI and formic acid followed by treatment with potassium carbonate in methanol as solvent. After column chromatography the enaminones can be obtained in very good yields (43% to 96%).

Limitations

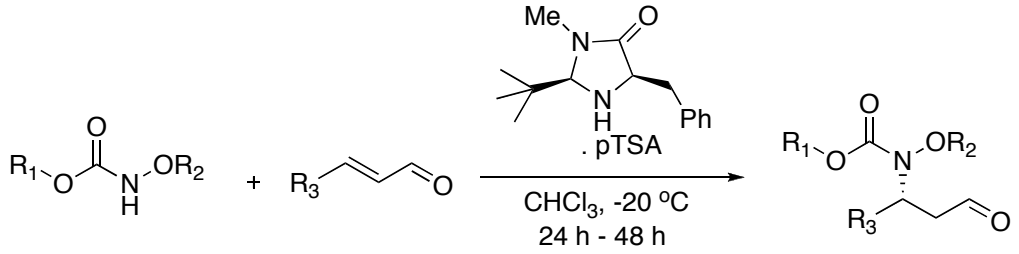
The Ishihara method does not provide particularly high selectivity and hence the ee is compromised and the yields are also not good. Although the method developed by Comins is by far the most frequently employed to synthesize chiral asymmetric enaminones, it does not provide a direct route for the synthesis of enaminones. The Georg method requires β-amino acids as starting materials. Although these are readily available, they can be as expensive as $200/gram. The alternate route is to generate them by homologation. In this case, although the homologation method is readily scalable and calls for relatively inexpensive starting materials, the process gives moderate yields. The method requires large quantities of diazomethane that is extremely flammable and hazardous to handle. With respect to the diversity point of view the availability of amino acids is limited. So there is a limitation on the variety of products one can obtain.

2. Strategy

Optically active β-amino acids have been of great interest to medicinal chemists all over the world due to their presence in various natural products.[12] Their versatility allows a number of chemical transformations that can be performed to convert them into yet more useful intermediates. Although homologation of α-amino acids is a direct method to generate the β-amino acids, the conjugate addition of amines or equivalent nucleophiles to the α,β-unsaturated carbonyl compounds is an alternate practical and flexible strategy for generating β-amino acid-like molecules.[13, 14] A number of recent publications focusing on the same topic include the Michael addition of aldoximes,[15] hydrazoic acid,[16] trimethylsilyl azide[17] and hydroxylamines.[18] Often these reactions are promoted by catalytic quantities of chiral metal complexes[15-18] and simple peptides.[16] For reactions with weaker nitrogen nucleophiles like carbamates, catalytic activation of α,β-unsaturated carbonyl compounds is required and is more difficult.

In 2005, David MacMillan developed a strategy of generating β-amino aldehydes and the corresponding β-amino acids by enantioselective organocatalytic conjugate addition of *N*-silyloxycarbamate nucleophiles to α,β-unsaturated aldehydes (Scheme 4).[19]

Scheme 4. Enantioselective Organocatalytic Amine Conjugate Addition

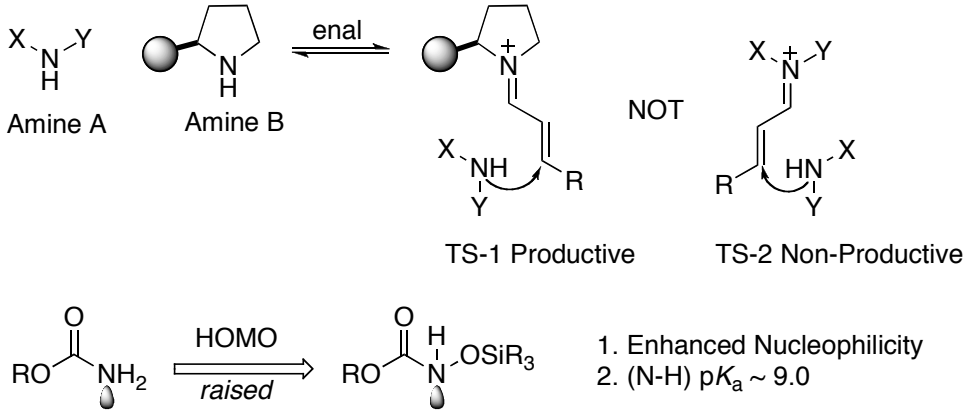


R_1 = t-Bu, Bn, 9-Fluorenylmethyl
R_2 = TBS, TBDPS

The synthesis employed two different types of amines, amine A and amine B (Figure 4). The amine A was chosen as a nucleophilic component. *N*-silyloxycarbamates were found to be suitable as amine A on the basis of two criteria:

1) The α-effect due to the *N-O* functionality will increase nucleophilicity at the nitrogen center, while the carbamate functionality will furnish effectively non-basic β-amino aldehydes (silyloxycarbamate N-H, estimated pK_a ~ 9.0). [19, 20]
2) They will selectively function as 1,4-addition nucleophiles and will not participate in the iminium activation.

Figure 4. Selectivity of Amines and Nucleophilicity Enhancement of Carbamate by α-Effect

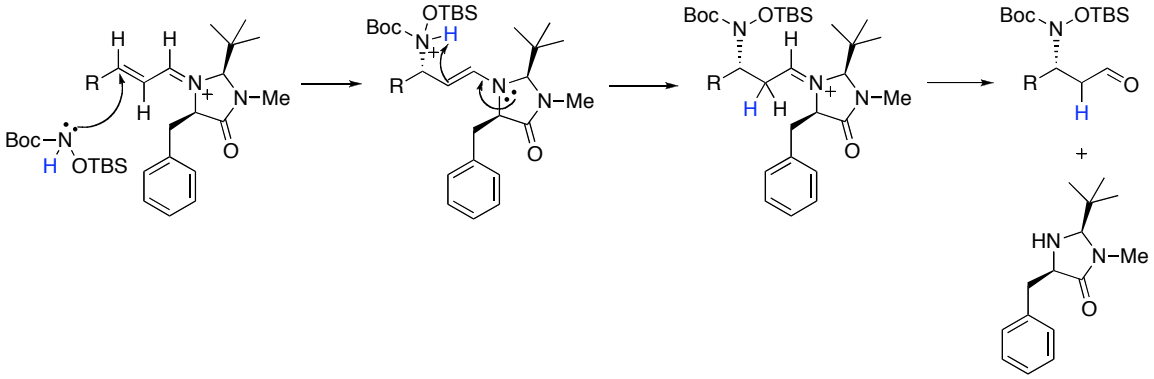


Amine B was selected as an iminium activating catalyst. An imidazolidinone amine was found to be useful because of its role in asymmetric iminium activation of enals and enones while not participating in the 1,4-addition.[21] Figure 4 shows the function of both amine A and amine B. The transition state TS-1 is desired in order to obtain the required products. In TS-1, the amine B selectively forms an iminium species with the α,β-unsaturated aldehydes. Then the amine A, selectively acting as a nucleophile, is added in a Michael fashion onto the iminium species. In the undesirable transition state TS-2, amine A acts as a nucleophile as well forming iminium species with the enal. Since this type of transition state is undesirable, the design of amine A becomes extremely important. Figure 4 also explains the change in the nucleophilicity at the nitrogen center. Due to the α-effect promoted by the oxygen atom attached directly to the nitrogen atom, the energy of the Highest Occupied Molecular Orbital (HOMO) on the nitrogen atom is raised. Hence the *N*-silyloxycarbamate is more nucleophilic than the corresponding carbamate molecule. But again, due to the presence of the carboxylate functionality on the nitrogen atom, the nucleophilicity is controlled and the resultant *N*-silyloxycarbamate molecule is effectively non-basic, with the pK_a of N-H ~ 9.0 in the *N*-silyloxycarbamate molecules.[20]

Choosing the specific nucleophiles and catalyst ensured reaction progress under kinetic (asymmetric) control with stereodefining nitrogen atom addition accompanied by irreversible loss of the nucleophile's proton. This avoided the possibility of an equilibrium-controlled process with reversible addition of the

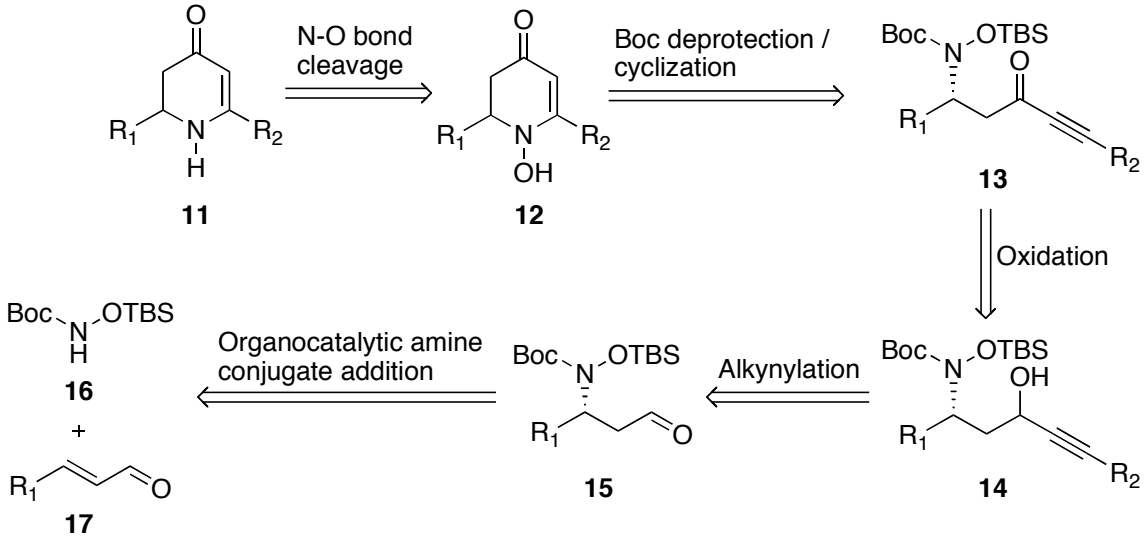
nitrogen nucleophile and hence generating racemic products. The Figure 5 shows a detailed mechanism for conjugate addition of nucleophilic the *N*-silyloxycarbamate to α,β-unsaturated aldehydes.

Figure 5. Mechanism of Conjugate Addition



We decided to employ this well developed strategy to generate β-amino aldehydes for the synthesis of enaminones. A retrosynthetic analysis is summarized in Scheme 5.

Scheme 5. Retrosynthetic Analysis



Our approach involves formation of *N*-oxygenated enaminones **12**, which can be subjected to *N*-*O* bond cleavage conditions such as using SmI_2 or Zn/AcOH in order to generate the enaminones **11**. The *N*-oxy enaminones **12** can be generated by one-pot Boc-deprotection/cyclization of the ynone intermediates **13**. This can be achieved by using the conditions for enaminone generation that were previously developed in the Georg group.[11] The ynones **13** can be synthesized by oxidation of the corresponding propargyl alcohols **14**. The propargyl alcohols **14** can be constructed by nucleophilic addition of alkynyl nucleophiles (alkynyl Grignard reagents or alkynyl lithium reagents) to the β-amino aldehydes **15**. The β-amino aldehydes **15** can be synthesized according to MacMillan's protocol. Hence within five steps the enaminones can be generated. The striking feature of these enaminones is the substituent diversity one can obtain with this approach. Instead of starting with only 20 α-amino acids, we can generate nearly infinite number of compounds from a large variety of enals and alkynes. Also, we avoid using hazardous materials like diazomethane. This synthetic plan can render a library of enaminones and this is of high interest to a research program in natural product and diversity-oriented synthesis (DOS).[8]

3. Synthesis, Results and Discussions

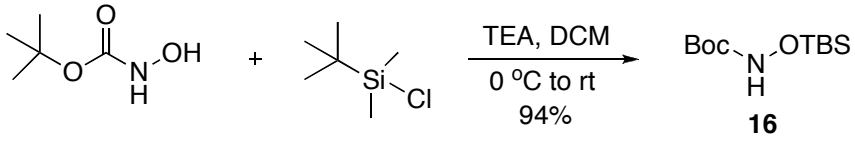
3.1 Synthesis of β-Amino Aldehydes 15[19]

The β-amino aldehydes were prepared according to the strategy developed by David MacMillan. The synthesis of these aldehydes required *tert*-butyl-(*tert*-butyldimethylsilyloxy)carbamate (**16**) and α,β-unsaturated aldehydes **17** as starting materials.

3.1.1 Synthesis of *tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate (16)

The *N*-silyloxycarbamate nucleophile was synthesized starting with commercially available *tert*-butyl-*N*-hydroxycarbamate and TBS chloride (Scheme 6). *tert*-Butyl-*N*-hydroxycarbamate, TBS-chloride and triethylamine were stirred overnight in CH_2Cl_2 as solvent. After work-up and column chromatography, *tert*-butyl-(*tert*-butyldimethylsilyloxy)carbamate (**16**) was obtained in 94% as a pure, low melting solid (reported yield = 92%).

Scheme 6

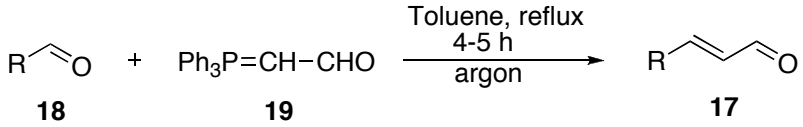


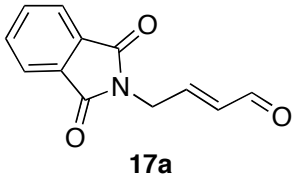
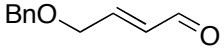
3.1.2 Synthesis of α,β-Unsaturated Aldehydes 17

Some of the α,β-unsaturated aldehydes such as 2-hexenal and crotonaldehyde required for preparing β-amino aldehydes, were available commercially. But in order

to introduce diversity, we decided to synthesize other enals starting from the corresponding aldehydes. In order to achieve this, we followed a strategy developed by Zhang et al.[21] The starting aldehydes **18** and triphenylphosphoranylidene acetaldehyde (**19**) were refluxed in toluene under inert argon atmosphere (Table 1). After column chromatography, pure α,β-unsaturated aldehydes (**17a** and **17b**) were obtained in good (81% and 85% respectively) yields.

Table 1. Synthesis of α,β-Unsaturated Aldehydes **17**

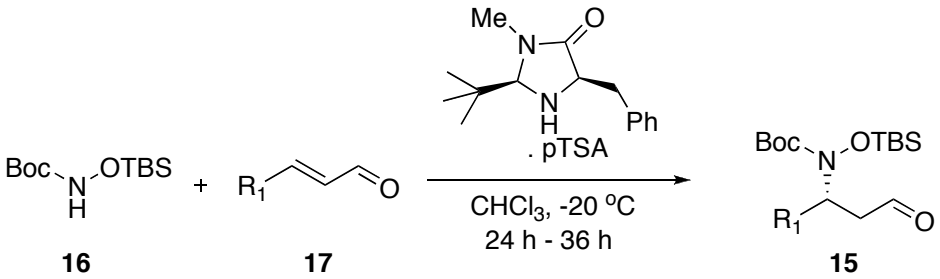


Entry	R	Product	Yield (%)
1	PhthN-CH_2	 **17a**	81
2	BnO-CH_2	 **17b**	85

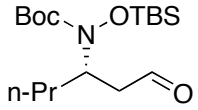
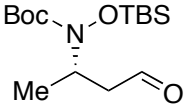
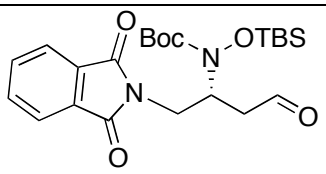
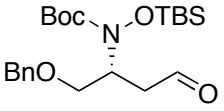
3.1.3 Synthesis of β-Amino Aldehydes 15

The next step was to synthesize β-amino aldehydes. Using MacMillan's protocol,[19] the corresponding β-amino aldehydes were synthesized (Table 2).

Table 2. Synthesis β-Amino Aldehydes



16 **17** **15**

Entry	R_1	Product	Yield (%)	ee (%)	Time (h)
1	n-Pr	 **15a**	73	92	24
2	Me	 **15b**	75	--*	24
3	PhthN-CH_2	 **15c**	39	87	36
4	BnO-CH_2	 **15d**	68	--*	36

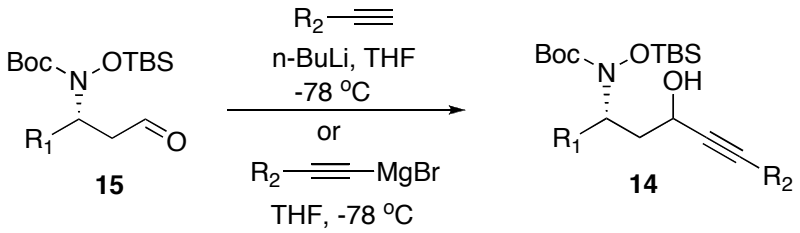
* to be determined

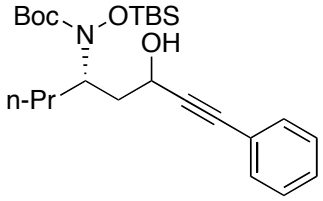
The required β-amino aldehydes were obtained in good yields. The enantiomeric excess (%) values of the aldehydes were determined using different strategies. For aldehyde **15a**, the optical rotation exactly matched with the literature value[19] ($[\alpha]^{D}_{25}$ = -1.52 (c = 0.500, $CHCl_3$)) and hence it was concluded that the % ee value would be the same as given in the literature (92%). The aldehyde **15c**, was further treated with acetone-water (4:1) and *p*TSA.H_2O for 12 hours. After usual workup and purification by column chromatography (20% EtOAc/hexanes), pure (3*S*,5*S*)-tert-Butyl-3-(*N*-methylphthalimido)-5-hydroxyisoxazolidine-2-carboxylate was isolated. Optical rotation value of this sample exactly matched with that of the literature value ($[\alpha]^{D}_{25}$ = -60.0 (c = 0.600, $CHCl_3$)) and hence it was concluded that the % ee value would be the same as given in the literature (87%). We first tried to separate the enantiomers of aldehydes **15b** and **15d** by using chiral HPLC (on a Chiralcel-OD column), but we found them to be inseparable. Therefore, both the aldehydes were converted to the corresponding alcohols by $NaBH_4$ reduction. These were then coupled with the Mosher's acid chloride to yield diastereomeric mixtures of Mosher esters. The ^{19}F NMR analysis was carried out on these esters. Due to some ambiguity with respect to the NMR signals, determination of %ee was not possible. Our future plan includes deprotection of the Boc group from the aldehydes and subsequent protection with the Cbz group. This will render compounds that are known in the literature, and hence by merely comparing the optical rotation, the %ee value could be determined.

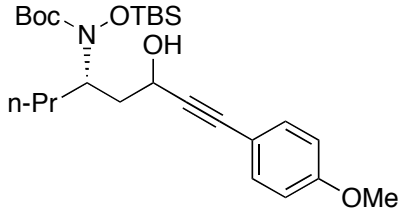
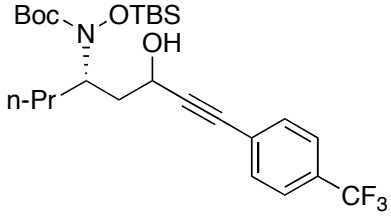
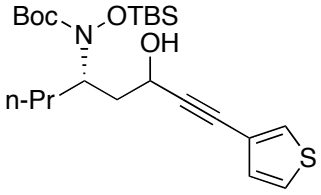
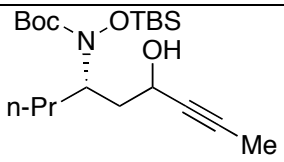
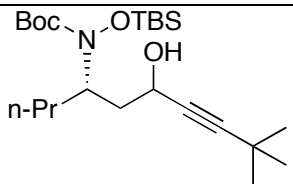
3.2 Synthesis of Propargyl Alcohols 14

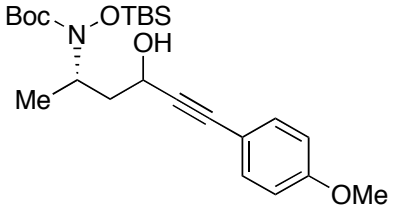
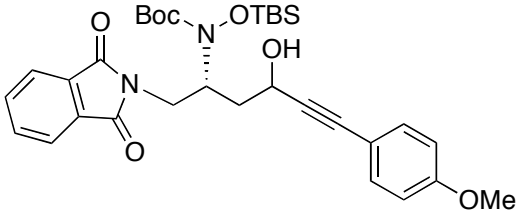
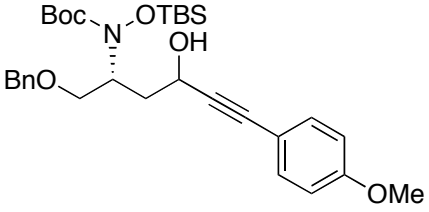
The β-amino aldehydes were next reacted with various alkynyl nucleophiles. We screened several commercially available acetylenes. Active alkynyl nucleophiles can be generated by a combination of alkyl or aryl terminal acetylenes and a strong base like n-BuLi. Alternatively alkynyl Grignard reagents can be used. We decided to employ both ways as per the availability of the reagents. The alkynyl nucleophile was either generated or used directly (if commercially available) in THF. A THF solution of β-amino aldehyde was added to the nucleophile solution at -78 °C and stirred for 4-5 h. The NMR spectra of the reaction products revealed that the alcohols were obtained as 1:1 mixture of two diastereomers. Table 3 shows the structures of the propargyl alcohols synthesized.

Table 3. Synthesis of Propargyl Alcohols **14**



Entry	R_1	R_2	Product	Yield (%)
1	n-Pr	Ph	 **14a**	64

2	n-Pr	4-MeO(C_6H_4)	 **14b**	33
3	n-Pr	4-CF_3(C_6H_4)	 **14c**	83
4	n-Pr	3-thiophenyl	 **14d**	26
5	n-Pr	Me	 **14e**	55
6	n-Pr	t-Bu	 **14f**	70

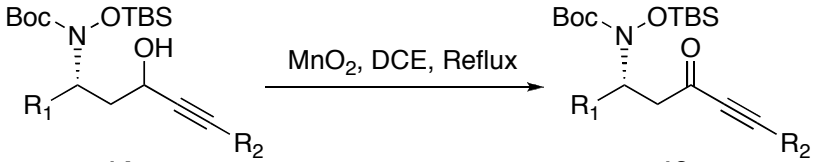
7	Me	4-MeO(C_6H_4)	 **14g**	59
8	PhthN-CH_2	4-MeO(C_6H_4)	 **14h**	21
9	BnO-CH_2	4-MeO(C_6H_4)	 **14i**	46

3.3 Synthesis of Ynones 13

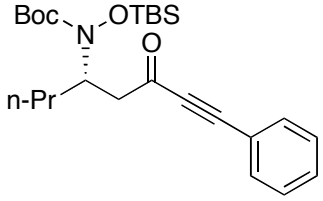
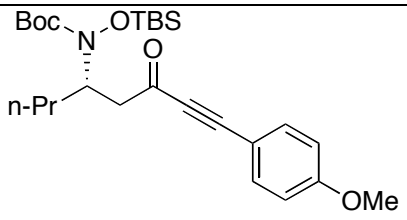
The next step was the oxidation of the propargyl alcohols to convert them into alkynyl ketones. There are several methods to achieve this transformation, such as Dess-Martin, Swern, or the use of chromium reagents or MnO_2. We decided to employ MnO_2 oxidation of our propargyl alcohols. CH_2Cl_2 was chosen as a solvent. However, even after an overnight stirring of a propargyl alcohol and excess MnO_2 in refluxing CH_2Cl_2, the reaction did not go to completion (less than 50% as shown by TLC). We therefore employed a higher boiling solvent, 1,2-dichloroethane (DCE),

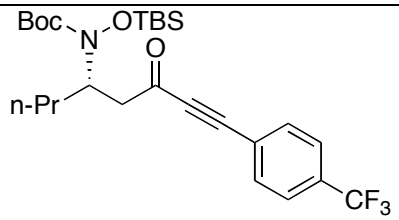
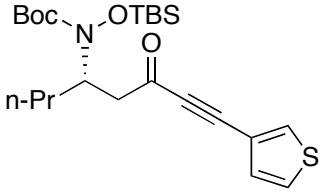
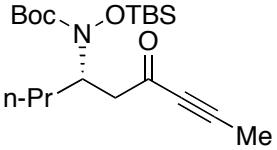
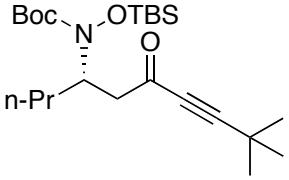
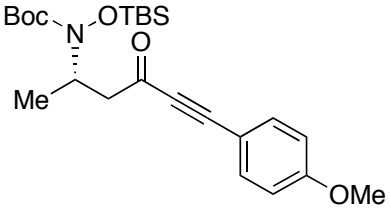
which boils around 115 °C and possesses similar characteristics to CH_2Cl_2. We dissolved our propargyl alcohols in DCE, added excess of MnO_2 and refluxed the mixture overnight. Table 4 shows the structures and yields of the various ynones.

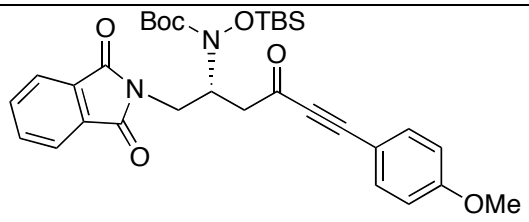
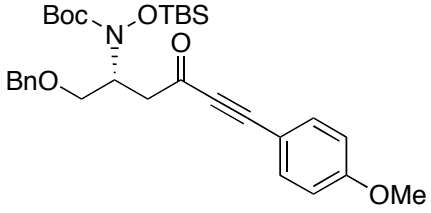
Table 4. Synthesis of Ynones **13**



14 **13**

Entry	R_1	R_2	Product	Yield (%)
1	n-Pr	Ph	 **13a**	70
2	n-Pr	4-MeO(C_6H_4)	 **13b**	68

3	n-Pr	4-$CF_3(C_6H_4)$	 **13c**	90
4	n-Pr	3-thiophenyl	 **13d**	100
5	n-Pr	Me	 **13e**	77
6	n-Pr	t-Bu	 **13f**	90
7	Me	4-MeO(C_6H_4)	 **13g**	54

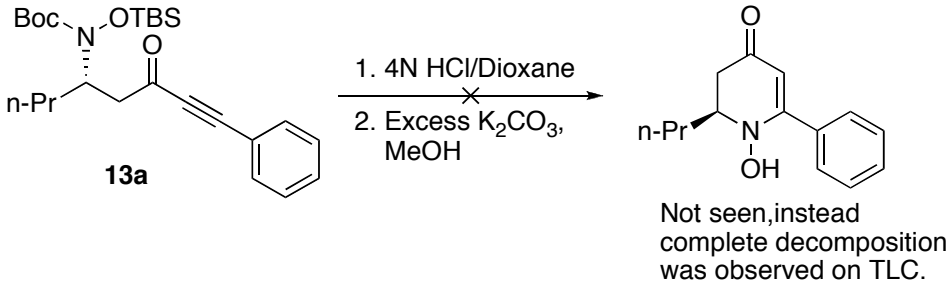
8	PhthN-CH_2	4-MeO(C_6H_4)	 **13h**	100
9	BnO-CH_2	4-MeO(C_6H_4)	 **13i**	88

In most of the cases, the yields were good. All the ynones were used crude for the next reactions, since the TLC showed a single, clear spot and the NMR showed more than 95% purity.

3.4 Synthesis of *N*-oxy Enaminones 12

The next step was a one step Boc deprotection/cyclization. The ynone (*S*)-*tert*-butyl *tert*-butyldimethylsilyloxy(6-oxo-8-phenyloct-7-yn-4-yl)carbamate (**13a**) was subjected to the cyclization conditions developed previously in the Georg laboratory. After treatment of **13a** with 4N HCl/Dioxane, MeOH and excess K_2CO_3 were added (Scheme 7).

Scheme 7. Unsuccessful Attempt of Cyclization



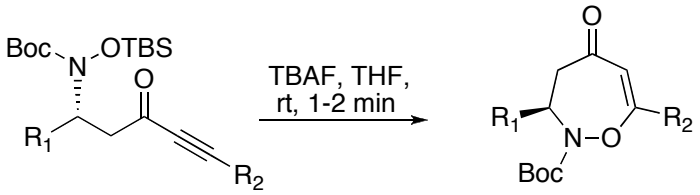
After the usual workup, the TLC showed complete decomposition of the substrate. This showed that the cyclization conditions are not suitable for these types of substrates. Repeating the experiments several times, with the same ynone (**13a**) and other ynones, gave the same results. One of the possible reasons for this observation was the use of strong 4N HCl. Probably the highly concentrated protic acid like HCl, deprotected both the Boc and the TBS group and decomposed the product. In the course of the reaction, both Boc and TBS can be removed simultaneously, creating complex mixture of products. Although, we had anticipated the removal of the TBS group in the course of the reaction, we had not expected the simultaneous deprotection.

3.5 Synthesis of Novel 7-Membered Oxazepinones 20

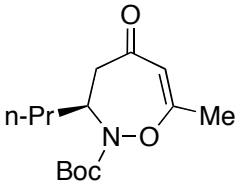
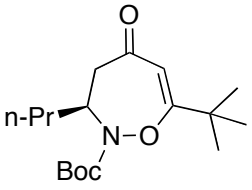
Taking into consideration the fact that both the Boc and TBS group can be deprotected by strong acid, we decided to use an orthogonal strategy, wherein only one group will be deprotected at a time. After a literature survey, we found that most of the methods deprotect the Boc group by acidic conditions, to which the TBS group

is very sensitive as well. We therefore decided to keep the Boc group and deprotect the TBS group first. We thought this would render us with either a free hydroxyl if quenched by a proton, which could then be reprotected with another protecting group. The other possibility was the 7-endo-dig addition of the free Boc-*N*-*O* anion onto the triple bond yielding the unusual and novel *N*-*O*-heptacyclic enones a.k.a. oxazepinones. We dissolved the ynone (*S*)-*tert*-butyl *tert*-butyldimethylsilyloxy(6-oxonon-7-yn-4-yl)carbamate (**13e**) in THF and to this mixture, 1M TBAF solution in THF was slowly added in a dropwise manner at room temperature (Table 5).

Table 5. Synthesis of Novel Oxazepinones **20**



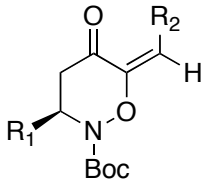
13 **20**

Entry	R_1	R_2	Product	Yield (%)
1	n-Pr	Me	 **20e**	73
2	n-Pr	t-Bu	 **20f**	52

Within few seconds after complete addition of the TBAF solution, the color of the reaction mixture changed from light yellow to dark brown. The TLC analysis of this mixture at this stage showed complete absence of the starting ynone and a single spot of the product. We decided to quench the reaction with silica gel as a very mild source of protons. After column chromatography, the product was obtained in 73% yield. NMR analysis of this yet unknown product **20e** revealed that it was indeed the novel heptacyclic oxazepinone **20e**. We subjected ynone (*S*)-*tert*-butyl *tert*-butyldimethylsilyloxy(9,9-dimethyl-6-oxodec-7-yn-4-yl)carbamate (**13f)** to similar conditions and found that the product obtained this time was again a novel heptacyclic enone **20f**. Table 5 shows the structures of products and yields. We next subjected the ynone (*S*)-*tert*-butyl *tert*-butyldimethylsilyloxy(6-oxo-8-phenyloct-7-yn-4-yl)carbamate (**13a**) (Table 6) to the same one pot TBS deprotection/cyclization conditions expecting to obtain another oxazepinone. We observed an interesting trend in this conversion. For all the cases along with the case of **13a**, when R_2 was aromatic, the ^{1}H NMR spectra were found to be characteristic. The olefinic proton was found around 5.81-5.95 ppm in 1H NMR spectra, while for previously synthesized oxazepinones, **20e** and **20f**, the olefinic protons were seen around 5.31-5.33 ppm. Also, the ortho-protons of the phenyl ring and thiophene were found much more deshielded than they would be in a normal case. Therefore we initially thought that the ynones bearing aromatic R_2 substituents might have cyclized by 6-exo-dig mechanism to 6-membered oxa-piperidinones (**21**) possessing *E*-stereochemistry (Figure 6). A logical explanation for this observation was thought to be the

anisotropic effect of the carbonyl group. If the aromatic ring attached to the double bond were on the same side as that of the carbonyl group, then the ortho-protons would be more deshielded due to the polarizable C=O bond. Generally, ortho protons of a phenyl ring (or substituted phenyl ring) would show a chemical shift at 7.43-7.55 ppm, but in our cases the ortho protons of the aromatic substituents showed a chemical shift at 7.72-8.07 ppm depending upon the substituent on the aromatic ring.

Figure 6. Structure of 6-membered oxa-piperidinones **21**



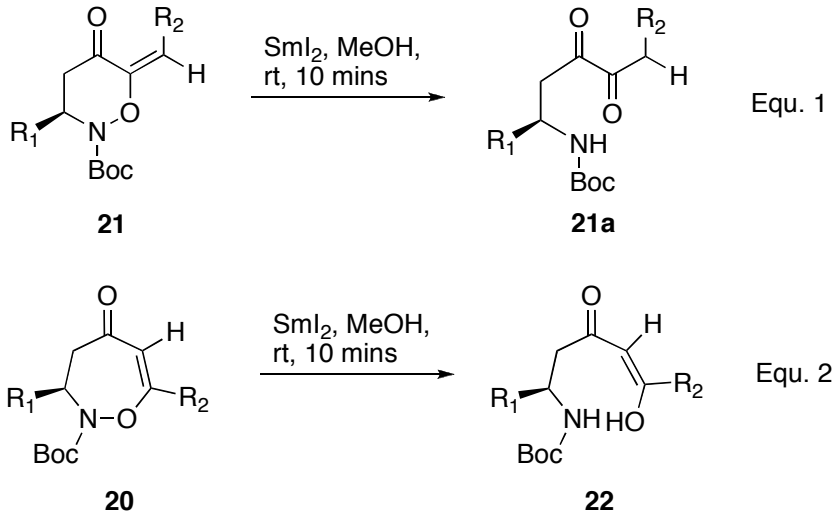
21

R_2 = Aromatic

But, on further studies of both the ^{13}C and ^{1}H NMR spectra, it was found that these compounds are all 7-membered oxazepinones **20**. In order to confirm the structures of these compounds we subjected them to reductive *N-O* bond cleavage conditions. A ^{1}H and ^{13}C NMR analysis of the cleaved products was carried out. If the starting compounds were indeed 6-membered oxa-piperidinones **21** then the reaction products **21a** should have been the 1,2-diketones (Figure 7). But since we could clearly see the presence of an enol proton and an olefinic proton in the ^{1}H NMR, it was more likely that the cleaved products were 1,3-diketones **22**, in which case it is possible for them to exist in the ketoenol forms. The olefinic protons in these *N-O* bond cleaved compounds **22** were seen at around 6.06 ppm in the ^{1}H NMR and the ortho protons of

the aromatic rings were found more deshielded (downfield) exactly as they were found in starting materials.

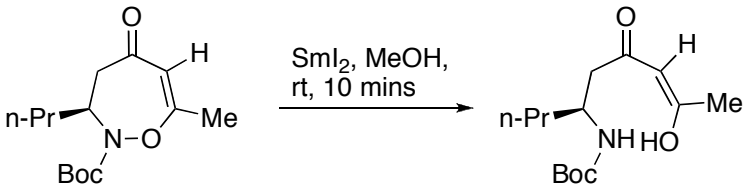
Figure 7. Reductive Cleavage of the *N-O* bond



Only one ketone carbonyl carbon was clearly seen in the ^{13}C NMR at around 192 ppm. The olefinic carbon bearing both an aromatic substituent and a hydroxyl group was also clearly seen at around 179 ppm. The other olefinic carbon bearing a proton was seen around 97 ppm. We compared the NMR analyses of our 1,3-diketones to the structurally similar β-keto-trimethylsilyl-enol-ethers.[23] We found that the chemical shifts of protons and carbons of our 1,3-diketones were comparable with the literature values. Hence, we concluded that all cyclization products are oxazepinones. We also reconfirmed the structure of oxazepinone **20e** by NMR analysis of its corresponding *N-O* cleaved structure (Figure 8). In this case the ^{1}H NMR of a methyl group attached to the olefinic carbon was observed at around 2.1 ppm as a singlet, which indicated that the structure was indeed the 1,3-diketone. Had the starting cyclic product been a

6-membered oxa-piperidinone then the ^{1}H NMR of the *N-O* cleaved structure should have shown the methyl group as a triplet.

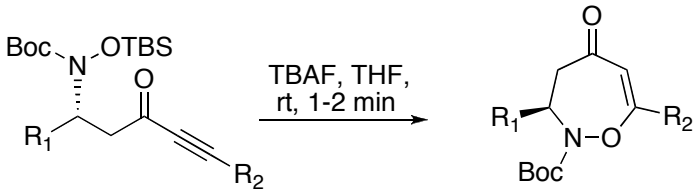
Figure 8. Reductive Cleavage of *N-O* bond of Oxazepinone **20e**



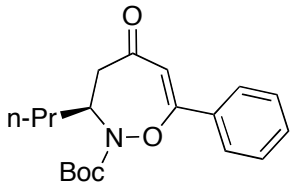
20e **22e**

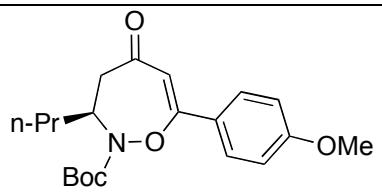
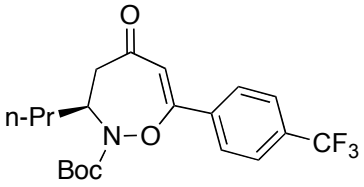
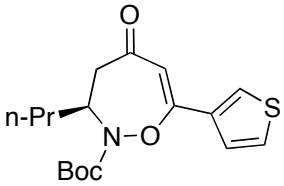
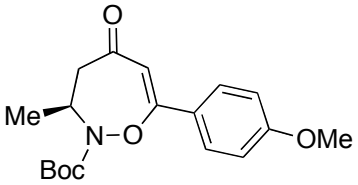
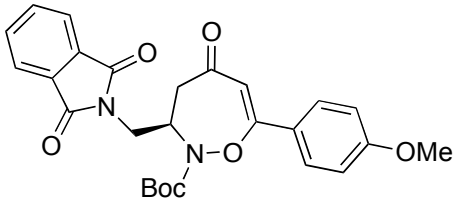
Table 6 shows the 7-membered oxazepinones **20** with aromatic R_2 substituents on the ynone functionality.

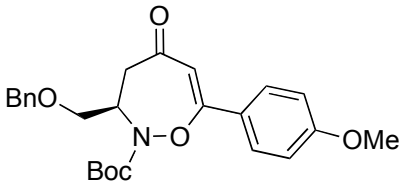
Table 6. Synthesis of Novel Oxazepinones **20**



13 **20**

Entry	**R_1**	**R_2**	**Product**	**Yield (%)**
1	n-Pr	Ph	 **20a**	77

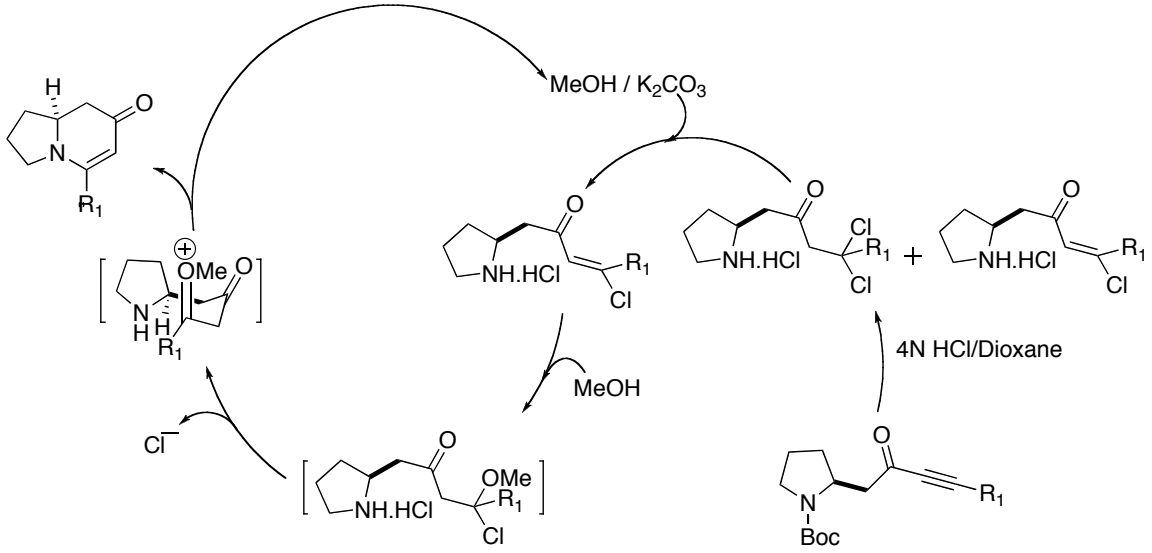
2	n-Pr	4-MeO(C_6H_4)	 **20b**	91
3	n-Pr	4-CF_3(C_6H_4)	 **20c**	23
4	n-Pr	3-thiophenyl	 **20d**	64
5	Me	4-MeO(C_6H_4)	 **20g**	44
6	PhthN-CH_2	4-MeO(C_6H_4)	 **20h**	43

7	BnO-CH_2	4-MeO(C_6H_4)	 **20i**	48

3.6 Proposed Mechanism of Cyclization

A mechanism for the cyclization of ynones to enaminones has been proposed by our group for the previously developed methodology (Scheme 8).[11]

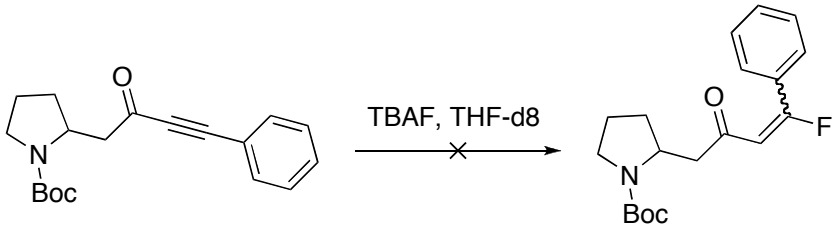
Scheme 8. Mechanism of Cyclization of Ynones to Enaminones



In this mechanism, the chloride anion was found to attack the triple bond of the ynone, forming either the vinyl chloride or the dichloride.[11] Methanol would act as a nucleophilic solvent and convert the monochloro and dichloro species into a geminal

methoxy chloro species. This intermediate would lead to the enaminone by losing the chloride anion. Based on this mechanism, we thought of adding fluoride anion to the β-hydroxylamino ynone. In order to confirm this mechanism, we carried out NMR studies. In this model study, 0.0500 g (0.159 mmol, 1.00 equiv) of *tert*-butyl 2-(2-oxo-4-phenylbut-3-ynyl)pyrrolidine-1-carboxylate **(substrate X)** was dissolved in THF-d8 (1.00 mL) in an NMR tube (Table 7).

Table 7. NMR Studies for Confirmation of the Mechanism of Cyclization



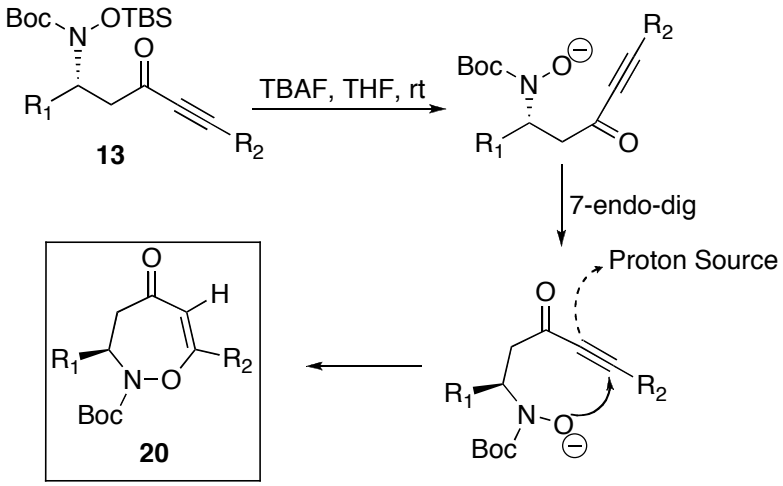
Substrate X **Product Y**

TBAF (equivs)	Observations
0	SM peaks
0.1	SM and TBAF peaks
0.3	SM and TBAF peaks
1	SM peaks started to fade away, large TBAF peaks
1.5	SM peaks almost faded away, no product peaks, large TBAF peaks
3	SM peaks completely faded away, no product peaks, large TBAF peaks

TBAF solution was added to this solution in increasing amounts. After every addition of a TBAF equivalent, the ^{1}H NMR spectrum of the mixture was recorded for identifying any formation of *tert*-butyl 2-(4-fluoro-2-oxo-4-phenylbut-3-enyl)pyrrolidine-1-carboxylate **product Y**. Table 7 summarizes the observations of the experiment. From the observations it was clear that the fluoride anion did not

attack the triple bond of the ynone. We are therefore proposing that the addition of TBAF to the ynone leads to a TBS deprotected intermediate (Scheme 9). This intermediate can cyclize in 7-endo-trig manner. The free oxygen anion can attack the triple bond in Michael fashion followed by quenching with a proton forming the 7-membered oxazepinones.

Scheme 9. Proposed Mechanism for Cyclization



3.7 Synthetic Utility of Oxazepinones

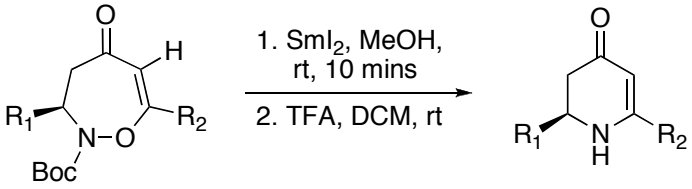
The newly formed 7-membered oxazepinones are structurally similar to the enaminones and therefore a variety of reactions can be performed with them. All the transformations that can be carried out on enaminones (Figure 1) should be possible with these compounds. This strategy can yield a wide number of large libraries. We decided to carry on a short 2-step transformation with our oxazepinones.

1. *N-O* bond cleavage
2. Boc deprotection

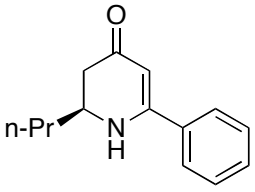
3.8 Synthesis of Enaminones 25

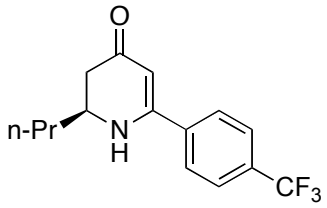
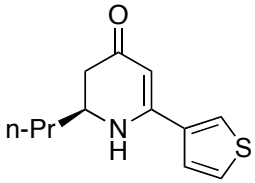
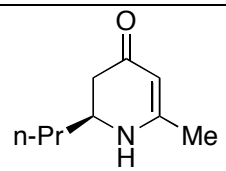
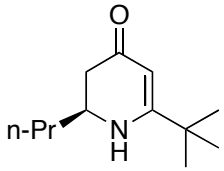
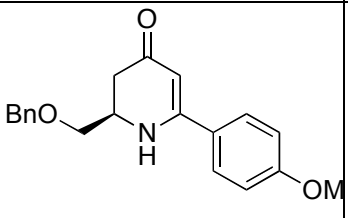
The oxazepinones **20** were subjected to reductive cleavage by treatment with SmI_2 and MeOH as solvent (Figure 7, Equ. 2). The product was generally not isolated and purified but instead was taken as a crude to the next step. The intermediates were subjected to a Boc-deprotection reaction. Table 8 shows the structures and yields of the products. After usual work-up with a saturated solution of Na_2CO_3 and brine, the TLC analysis of the solution showed presence of only one compound. ^1H and ^{13}C NMR analysis revealed the formation of enaminones **25**.

Table 8. Synthesis of Enaminones **25**



20 **25**

Entry	R_1	R_2	Product	Yield (%)
1	n-Pr	Ph	 **25a**	60

2	n-Pr	4-$CF_3(C_6H_4)$	 **25c**	78
3	n-Pr	3-thiophenyl	 **25d**	88
4	n-Pr	Me	 **25e**	100
5	n-Pr	t-Bu	 **25f**	100
6	BnO-CH_2	4-MeO(C_6H_4)	 **25i**	75

4. Conclusion

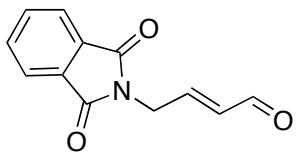
In conclusion, we have synthesized one known and one novel scaffold. The cyclization of β-hydroxylamino ynones **13** furnished novel oxazepinones **20**. TBS deprotection by TBAF promoted 7-endo-dig cyclization to furnish 3,4-dihydro-1,2-oxazepin-5(2*H*)-ones **20**. Reductive cleavage of the *N*-*O* bonds of intermediates **20** yielded 2,3-dihydropyridin-4-(1*H*)-ones (enaminones) **25**. Our original plan of preparing a library of enaminones is now possible via synthesis of novel oxazepinone intermediates. The newly prepared compounds constitute unique 7- and 6-membered scaffolds that can be used for the synthesis of diverse compound libraries. Additional chemical transformations such as nucleophilic addition to the double bond, 1,2-addition, enolate alkylation and *N*-acylation can be carried out to obtain additional diverse chemotypes. The dihydropyridones intermediates **25** can be used to prepare important natural products such as the indolizidine alkaloids.[6,22] Our future plans include submission of these compounds for biological testing in the NIH's MLSCN.

5. Experimental Section

General Information:

All commercially available reagents and solvents were used without further purification. tert-Butyl hydroxycarbamate and all acetylenes were purchased from Sigma-Aldrich. All other chemicals and solvents were purchased from Acros Organics and Sigma-Aldrich. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Flash column chromatography was carried out on silica gel. TLC was conducted on silica gel 250 micron, F_{254} plates. ^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR instrument. Chemical shifts are reported in ppm with TMS as an internal standard (TMS: 0.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Bruker 100 MHz NMR spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as internal standard ($CDCl_3$: 77.2 ppm). High-resolution mass spectrometry was performed by the University of Minnesota Mass Spectroscopy Facility. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured on a Rudolph Research Analytical AUTOPOL® V polarimeter and concentration (c) is in g/100 mL.

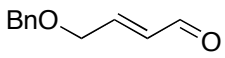
Experimental Procedures:



17a

(*E*)-4-(1,3-Dioxoisoindolin-2-yl)but-2-enal (17a): A toluene solution (80 mL) of

(triphenylphosphoranylidene)acetaldehyde (3.352 g, 10.57 mmol) and phthalimidoacetaldehyde (2.000 g, 10.57 mmol) was heated under reflux for 4-5 h under argon. The solvent was then removed under reduced pressure. Purification of the residue by silica gel column chromatography (30% EtOAc/hexane) provided the title compound as clear oil (1.8 g, 81% yield). IR (thin film) 1772, 1703, 1679, 1466, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (m, 2H), 6.14 (m, 1H), 6.83 (m, 1H), 7.76 (m, 2H), 7.89 (m, 2H), 9.56 (d, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.4, 123.6, 131.8, 133.1, 134.3, 148.9, 167.5, 192.5 ppm; HRMS calculated for ($C_{12}H_9NO_3$) required *m/z* [M+Na] 238.0480, found *m/z* 238.0484.



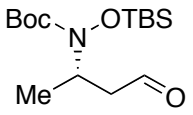
17b

(*E*)-4-(Benzyloxy)but-2-enal (17b): A toluene solution (80 mL) of (triphenylphosphoranylidene)acetaldehyde (4.222 g, 13.32 mmol) and benzyloxyacetaldehyde (2.000 g, 13.32 mmol) was heated under reflux for 4-5 h under argon. The solvent was then removed under reduced pressure. Purification of the residue by silica gel column chromatography (20% EtOAc/hexane) provided the title compound as clear oil (2.0 g, 85% yield). IR (thin film) 3088, 3064, 3032, 2731, 1690, 1642, 1454, 1027, 969, 740, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (m, 2H), 4.57 (s, 2H), 6.39 (m, 1H), 6.83 (m, 1H), 7.30-7.35 (m, 5H), 9.55 (d, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.5, 72.9, 127.6, 127.9, 128.4, 131.7, 137.4, 153.1, 193.2 ppm; HRMS calculated for ($C_{11}H_{12}O_2$) required *m/z* [M+Na] 199.0735, found

m/z 199.0734.

General Procedure for the Conjugate Amination of Aldehydes:

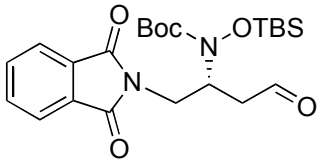
A round bottom flask equipped with a magnetic stir bar was charged with *p*TSA salt of (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (**cat. I**) and the appropriate enal in $CHCl_3$ was cooled to -20 °C. *tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate (**16**) was then added in one portion and the reaction mixture was stirred at -20 °C. Upon completion of the reaction as determined by TLC analysis (24-36 h), the products were isolated as below.



15b

(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(4-oxobutan-2-yl)carbamate (15b): Prepared using **cat. I.***p*TSA (176 mg, 0.404 mmol, 0.200 equiv), crotonaldehyde (0.507 mL, 6.06 mmol, 3.00 equiv) in $CHCl_3$ (6 mL) at –20 °C. *tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate (**16**) (500.0 mg, 2.021 mmol, 1.000 equiv) was added in one portion and the reaction was maintained at –20 °C for 24 h. Purification by silica gel column chromatography (10% Et_2O/hexane) provided the title compound as clear oil (480 mg, 75% yield, % ee). IR (thin film) 3430, 2958, 2931, 2849, 1728, 1473, 1461, 1388, 1368, 1251, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.95 (s, 9H), 1.24 (d, 3H), 1.48 (s, 9H), 2.60 (dd, 1H, J_1 = 7.1 and J_2 = 16.6 Hz), 2.80

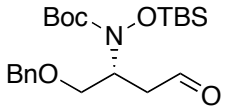
(dd, 1H, J_1 = 6.3 and J_2 = 16.6 Hz), 4.39 (m, 1H), 9.78 (t, 1H, J = 1.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.4, 17.8, 18.2, 25.8, 28.2, 34.7, 47.8, 54.3, 81.9, 158.6, 200.5 ppm; HRMS calculated for ($C_{15}H_{31}NO_4Si$) requires *m/z* [M+Na] 340.1920, found *m/z* 340.1916. $[\alpha]^{25}_D$ = +4.00 (*c* = 0.500, $CHCl_3$).



15c

(*R*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(1-(1,3-dioxoisoindolin-2-yl)-4-oxobutan-2-yl)carbamate (15c): Prepared according to the general procedure using **cat. I.***p*TSA (80.9 mg, 0.185 mmol, 0.200 equiv), (*E*)-4-(1,3-Dioxoisoindolin-2-yl)but-2-enal (**17a**) (0.598 mg, 2.78 mmol, 3.00 equiv) in $CHCl_3$ (2.78 mL) at –20 °C. *tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate (**16**) (229 mg, 0.926mmol, 1.00 equiv) was added in one portion and the reaction was maintained at –20 °C for 36 h. The reaction mixture was worked up according to the general procedure. Purification by silica gel column chromatography (30% EtOAc/hexane) provided the title compound as clear oil (168 mg, 39% yield, 87% ee). IR (thin film) 3442, 2945, 2909, 2849, 1719, 1395, 1364, 1252, 1169 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.14 (s, 3H), 0.83 (s, 9H), 1.42 (s, 9H), 2.70 (dd, 1H, J_1 = 6.1 and J_2 = 17.2 Hz), 2.98 (dd, 1H, J_1 = 7.8 and J_2 = 17.2 Hz), 3.79 (dd, 1H, J_1 = 6.4 and J_2 = 13.8 Hz), 4.11 (dd, 1H, J_1 = 9.7 and J_2 = 16.6 Hz), 4.59 (m, 1H), 7.68 (m, 2H), 7.81 (m, 2H), 9.73 (t, 1H, J = 1.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.8, 18.2, 25.8, 28.2, 39.0, 44.7, 56.8,

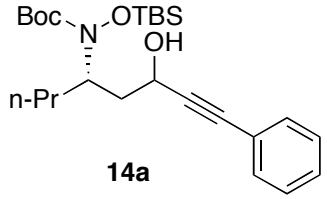
82.2, 123.4, 133.9, 134.2, 157.7, 168.2, 199.2 ppm; HRMS calculated for ($C_{23}H_{34}N_2O_6Si$) requires *m/z* [M+Na] 485.2084, found *m/z* 485.2089. $[\alpha]^{25}_D$ = -27.0 (*c* = 0.500, $CHCl_3$). The enantiomeric excess was determined by further derivatizing the title compound into (3*R*,5*S*)-*tert*-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-5-hydroxyisoxazolidine-2-carboxylate. The $[\alpha]^{25}_D$ value of this compound exactly matched with the literature value ($[\alpha]^{25}_D$ = -60.0 (*c* = 0.600, $CHCl_3$).



15d

(*R*)-*tert*-Butyl 1-(Benzyloxy)-4-oxobutan-2-yl(*tert*-butyldimethylsilyloxy)carbamate (15d): Prepared according to the general procedure using **cat. I.***p*TSA (176 mg, 0.404 mmol, 0.200 equiv), (*E*)-4-(Benzyloxy)but-2-enal (**17b**) (1.07 g, 6.06 mmol, 3.00 equiv) in $CHCl_3$ (6 mL) at –20 °C. *tert*-Butyl-(*tert*-butyldimethylsilyloxy)carbamate (**16**) (500.0 mg, 2.021 mmol, 1.000 equiv) was added in one portion and the reaction was maintained at –20 °C for 36 h. The reaction mixture was worked up according to the general procedure. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as clear oil (583 mg, 68% yield, % ee). IR (thin film) 3430, 2945, 2930, 2858, 1728, 1479, 1455, 1388, 1368, 1310, 1251, 1168, 1109, 841, 786, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.94 (s, 9H), 1.46 (s, 9H), 2.59 (dd, 1H, J_1 = 6.3 and J_2 = 16.5 Hz), 2.76 (dd, 1H, J_1 = 7.3 and J_2 = 16.5 Hz), 3.50 (dd, 1H,

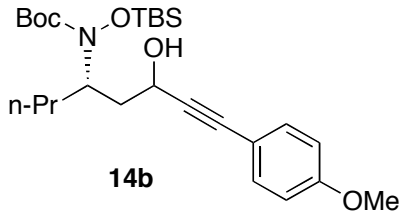
J_1 = 7.2 and J_2 = 9.4 Hz), 3.73 (dd, 1H, J_1 = 6.7 Hz and J_2 = 9.4 Hz), 4.51 (s, 2H), 4.61 (m, 1H), 7.31-7.34 (m, 5H), 9.75 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ – 4.5, 18.1, 26.0, 28.3, 43.8, 57.8, 68.5, 73.0, 82.0, 127.4, 128.5, 131.8, 137.9, 158.6, 199.9 ppm; HRMS calculated for ($C_{22}H_{37}NO_5Si$) requires *m/z* [M+Na] 446.2339, found *m/z* 446.2343. $[\alpha]^{25}_D$ = +1.80 (*c* = 0.500, $CHCl_3$).



14a

***tert*-Butyl *tert*-Butyldimethylsilyloxy((4*S*)-6-hydroxy-8-phenyloct-7-yn-4-yl)carbamate (14a):** Phenylacetylene (0.371 mL, 3.31 mmol, 1.50 equiv) was dissolved in dry THF (1 mL) and cooled to -78 °C. A solution of n-butyllithium (1.15 mL, 2.50 M in hexanes, 1.30 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15a** (760 mg, 2.19 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as pale yellow oil (631 mg, 64%). IR (thin film) 3350, 3028, 2925, 1708, 1600, 1384, 1364, 1158 758, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s,

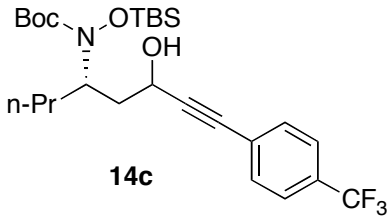
3H), 0.20 (s, 3H), 0.95 (m, 12H), 1.28-1.44 (m, 3H), 1.47 (s, 9H), 1.62-1.76 (m, 1H), 1.77-1.91 (m, 1H), 2.19-2.34 (m, 1H), 2.84 (br s, 1H), 3.96-4.10 (br m, 1H), 4.69 (m, 1H), 7.28-7.30 (m, 3H), 7.41-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.5, 13.9, 18.1, 19.9, 26.0, 28.2, 31.6, 40.6, 60.2, 61.5, 81.5, 84.7, 89.9, 122.8, 128.2, 131.7, 158.1 ppm; HRMS calculated for ($C_{25}H_{41}NO_4Si$) requires *m/z* [M+Na] 470.2703, found *m/z* 470.2692.



14b

***tert*-Butyl *tert*-Butyldimethylsilyloxy((4*S*)-6-hydroxy-8-(4-methoxyphenyl)oct-7-yn-4-yl)carbamate (14b):** 4-Ethynylanisole (0.291 mL, 2.17 mmol, 1.50 equiv) was dissolved in dry THF (1 mL) and cooled to -78 °C. A solution of n-butyllithium (0.75 mL, 2.5 M in hexanes, 1.3 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15a** (500 mg, 1.45 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as pale yellow oil (240 mg, 33%). IR (thin film) 3348, 2925, 2858,

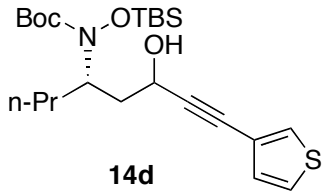
1708, 1598, 1384, 1364,1177, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.19 (s, 3H), 0.90-0.95 (m, 12H), 1.36-1.40 (m, 3H), 1.45 (s, 4H), 1.47 (s, 5H), 1.74-1.88 (m, 2H), 1.73-1.88 (m, 2H), 2.16-2.32 (m, 1H), 2.87 (br s, 1H), 3.79 (s, 3H), 3.97-4.09 (br m, 1H), 4.66 (m, 1H), 6.81 (d, 2H, *J* = 6.8 Hz), 7.36 (d, 2H, *J* = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.5, 13.9, 18.1, 19.9, 26.1, 28.3, 35.6, 40.7, 55.2, 60.2, 61.5, 81.6, 84.4, 88.6, 113.9, 114.9, 133.2, 158.3, 159.6 ppm; HRMS calculated for ($C_{25}H_{41}NO_4Si$) requires *m/z* [M+Na] 500.2808, found *m/z* 500.2799.



14c

***tert*-Butyl *tert*-Butyldimethylsilyloxy((4*S*)-6-hydroxy-8-(4-(trifluoromethyl)phenyl)oct-7-yn-4-yl)carbamate (14c):** 4-Ethynyl-α,α,α-trifluorotoluene (0.366 mL, 2.17 mmol, 1.50 equiv) was dissolved in dry THF (1 mL) and cooled to -78 °C. A solution of n-butyllithium (1.18 mL, 1.60 M in hexanes, 1.30 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15a** (500 mg, 1.45 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel column

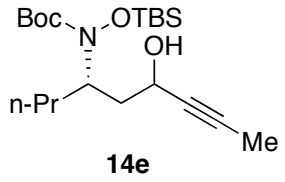
chromatography (20% Et_2O/hexane) provided the title compound as pale yellow oil (617 mg, 83%). IR (thin film) 3252, 2925, 2854, 1710, 1458, 1383, 1364, 1168, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 3H), 0.19 (s, 3H), 0.91-0.94 (m, 3H), 0.96(s, 9H), 1.45-1.49 (m, 12H), 1.75-1.92 (m, 2H), 2.19-2.35 (m, 1H), 3.74 (br s, 1H), 3.94-4.09 (br m, 1H), 4.70 (m, 1H), 7.52-7.56 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.4, 13.9, 18.1, 19.9, 26.0, 28.2, 35.7, 39.8, 60.1, 61.4, 81.6, 83.2, 92.4, 122.6, 125.2, 126.7, 130.2, 131.9, 158.4 ppm; HRMS calculated for ($C_{25}H_{41}NO_4Si$) requires *m/z* [M+Na] 538.2576, found *m/z* 538.2566.



14d

***tert*-Butyl *tert*-Butyldimethylsilyloxy((4*S*)-6-hydroxy-8-(thiophen-3-yl)oct-7-yn-4-yl)carbamate (14d):** 3-Ethynylthiophene (0.196 mL, 1.91 mmol, 1.50 equiv) was dissolved in dry THF (1 mL) and cooled to -78 °C. A solution of n-butyllithium (1.19 mL, 1.60 M in hexanes, 1.50 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15a** (440 mg, 1.27 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*.

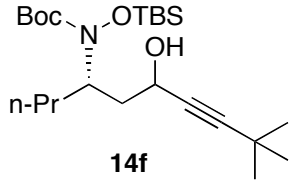
Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as pale yellow oil (149 mg, 26%). IR (thin film) 3258, 2960, 2932, 1708, 1456, 1383, 1369, 1158, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 6H), 0.91-0.95 (m, 3H), 0.96 (s, 9H), 1.41-1.46 (m, 3H), 1.48 (s, 9H), 1.79-1.89 (m, 2H), 2.21-2.23 (m, 1H), 3.57 (br s, 1H), 3.91-4.09 (br m, 1H), 4.65 (m, 1H), 7.08 (d, 1H, *J* = 5.0 Hz) 7.24 (m, 1H), 7.41 (d, 1H, *J* = 3.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.5, 13.9, 18.1, 19.9, 26.0, 28.3, 35.6, 39.9, 60.2, 61.5, 79.6, 81.9, 89.4, 121.9, 125.1, 128.8, 129.9, 158.8 ppm; HRMS calculated for ($C_{25}H_{41}NO_4Si$) requires *m/z* [M+Na] 476.2267, found *m/z* 476.2260.



14e

***tert*-Butyl *tert*-Butyldimethylsilyloxy((4*S*)-6-hydroxynon-7-yn-4-yl)carbamate (14e):** To a solution of **15a** (518 mg, 1.50 mmol, 1.00 equiv) in dry THF (30 mL), at -78 °C, under argon, 1-propynyl magnesium bromide (6.00 mmol, 0.500 M in tetrahydrofuran, 4.00 equiv) was slowly added. The reaction mixture was stirred at -78 °C and monitored by TLC. After 4-5 h when the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. Then it was diluted with ethyl ether, washed with brine, dried, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as yellow oil. (316.5 mg, 55%). IR (thin film) 3212, 2961, 2933, 1709, 1384, 1364, 1142 cm^{-1}; ^1H NMR (400 MHz,

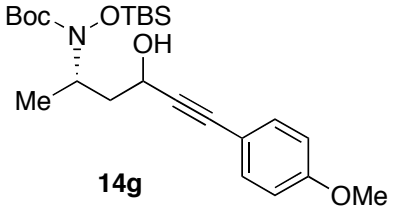
$CDCl_3$) δ 0.14 (s, 6H), 0.86-0.89 (m, 3H), 0.92 (s, 9H), 1.32-1.38 (m, 3H), 1.44 (s, 9H), 1.64-1.72 (m, 2H), 1.79 (s, 3H), 2.01-2.16 (m, 1H), 2.75 (s, 1H), 3.87-3.99 (br m, 1H), 4.39 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.4, 3.6, 13.7, 18.2, 19.9, 26.0, 28.3, 35.6, 40.8, 59.8, 61.1, 79.9, 80.6, 81.7, 158.3 ppm; HRMS calculated for ($C_{20}H_{39}NO_4Si$) requires *m/z* [M+Na] 408.2546, found *m/z* 408.2556.



14f

***tert*-Butyl *tert*-Butyldimethylsilyloxy((4*S*)-6-hydroxy-9,9-dimethyldec-7-yn-4-yl)carbamate (14f):** 3,3-Dimethyl-but-1-yn (0.217 mL, 1.73 mmol, 1.80 equiv) was dissolved in dry THF (1 mL) and cooled to -78 °C. A solution of n-butyllithium (1.08 mL, 1.60 M in hexanes, 1.80 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15a** (331 mg, 0.958 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (15% Et_2O/hexane) provided the title compound as pale yellow oil (277 mg, 70%). IR (thin film) 3224, 2964, 2934, 2874, 1709, 1459, 1383, 1369, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s,

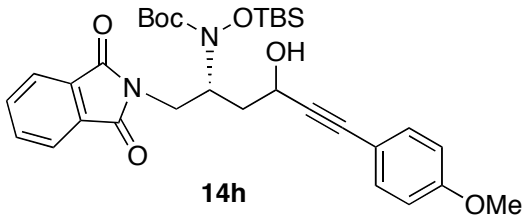
3H), 0.17 (s, 3H), 0.88-0.90 (m, 3H), 0.93 (s, 9H), 1.19 (s, 9H), 1.32-1.41 (m, 3H), 1.46 (s, 9H), 1.66-1.77 (m, 2H), 2.01-2.20 (m, 1H), 2.55 (br s, 1H), 3.82-3.98 (br m, 1H), 4.41 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.4, 13.9, 18.1, 19.9, 26.1, 27.3, 28.2, 31.0, 35.6, 41.2, 59.8, 61.2, 79.8, 81.6, 93.3, 158.3 ppm; HRMS calculated for ($C_{20}H_{39}NO_4Si$) requires *m/z* [M+Na] 450.3016, found *m/z* 450.3011.



14g

***tert*-Butyl *tert*-Butyldimethylsilyloxy((2*S*)-4-hydroxy-6-(4-methoxyphenyl)hex-5-yn-2-yl)carbamate (14g):** 4-Ethynylanisole (0.344 mL, 2.57 mmol, 1.70 equiv) was dissolved in dry THF (1 mL) and cooled to -78 °C. A solution of n-butyllithium (1.61 mL, 1.60 M in hexanes, 1.70 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15b** (480 mg, 1.51 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as pale yellow oil (400 mg, 59%). IR (thin film) 3348, 2928, 1711, 1598, 1384, 1364, 1177, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 6H), 0.96

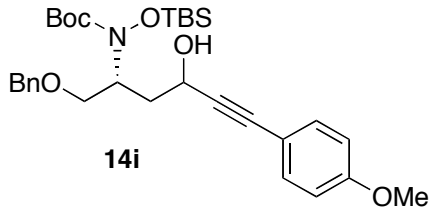
(s, 9H), 1.31 (d, 3H J = 6.9 Hz), 1.48 (s, 5H), 1.49 (s, 4H), 1.81-1.95 (m, 1H), 2.24-2.34 (m, 1H), 3.80 (s, 3H), 4.05-4.25(br m, 1H), 4.64 (m, 1H), 6.81 (d, 2H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5, 18.0, 18.5, 26.0, 28.3, 41.9, 55.2, 60.2, 61.2, 81.6, 84.5, 88.2, 113.8, 114.9, 133.1, 158.4, 159.6 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 472.2495, found *m/z* 472.2490.



14h

***tert*-Butyl *tert*-Butyldimethylsilyloxy((2*R*)-1-(1,3-dioxoisoindolin-2-yl)-4-hydroxy-6-(4-methoxyphenyl)hex-5-yn-2-yl)carbamate (14h):** 4-Ethynylanisole (0.052 mL, 0.39 mmol, 1.2 equiv) was dissolved in dry THF (10 mL) and cooled to -78 °C. A solution of Lithium bis(trimethylsilyl)amide (0.42 mL, 1.0 M in tetrahydrofuran, 1.3 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15c** (150 mg, 0.324 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% EtOAc/hexane) provided the title compound as pale

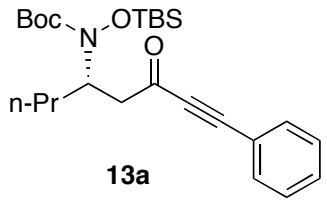
yellow oil (40 mg, 21%). IR (thin film) 3352, 2900, 1711, 1667, 1384, 1364,1177, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 6H), 0.86 (s, 4H), 0.88 (s, 5H), 1.42 (s, 4H), 1.43 (s, 5H), 1.87-2.02 (m, 1H), 2.40-2.47 (m, 1H), 3.80 (s, 3H), 3.86-4.04 (m, 1H), 4.09-4.29 (m, 1H), 4.29-4.37 (br m, 1H), 4.75 (m, 1H), 6.80 (d, 2H, *J* = 8.9 Hz), 7.31 (d, 2H, *J* = 8.9 Hz), 7.69 (m, 2H), 7.82 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, 17.9, 25.8, 28.1, 37.5, 40.5, 55.2, 60.4, 61.4, 82.4, 85.0, 87.9, 113.8, 123.3, 132.1, 133.1, 133.9, 157.6, 159.5, 168.0 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 617.2659, found *m/z* 617.2651.



14i

***tert*-Butyl (2*R*)-1-(Benzyloxy)-4-hydroxy-6-(4-methoxyphenyl)hex-5-yn-2-yl(*tert*-butyldimethylsilyloxy)carbamate (14i):** 4-Ethynylanisole (0.152 mL, 1.13 mmol, 1.20 equiv) was dissolved in dry THF (1 mL) and cooled to -78 °C. A solution of n-butyllithium (1.23 mL, 1.60 M in hexanes, 1.30 equiv) was then added drop wise. The mixture was stirred for 30 min at -78 °C and then **15d** (400 mg, 0.944 mmol, 1.00 equiv) was slowly added. The mixture was stirred for 4-5 h. When the reaction was complete as indicated by TLC, the mixture was quenched by adding aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water then with brine, dried over anhydrous magnesium sulfate, filtered and

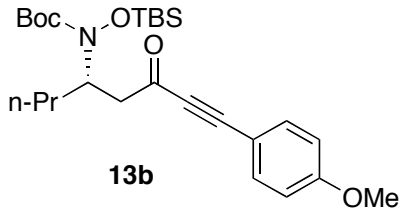
concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as pale yellow oil (240 mg, 46%). IR (thin film) 3350, 2967, 2900, 2833, 1713, 1384, 1364,1178, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 2H), 0.19 (s, 4H), 0.95 (s, 9H), 1.44 (s, 5H), 1.46 (s, 4H), 1.90-2.08 (m, 1H), 2.19-2.29 (m, 1H), 3.24 (br s, 1H), 3.55-3.66 (m, 1H), 3.75-3.83 (m, 1H), 3.80 (s, 3H), 4.19-4.35 (m, 1H), 4.54-4.56 (m, 2H), 4.74 (m, 1H), 6.81 (d, 2H, J= 8.8 Hz), 7.32-7.36 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.6, 18.0, 26.0, 28.2, 38.1, 55.2, 60.4, 61.2, 71.0, 73.0, 81.8, 84.7, 88.2, 113.8, 114.9, 125.9, 127.6, 128.3, 133.1, 137.9, 158.5, 159.6 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 578.2914, found *m/z* 578.2909.



13a

(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(6-oxo-8-phenyloct-7-yn-4-yl)carbamate (13a): Compound **14a** (0.622 g, 1.39 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (37 mL) and activated MnO_2 (3.07 g, 41.7 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (432 mg, 70%). IR (thin film) 3069, 3026, 2203, 1690, 1384, 1364, 1158, 758, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 3H), 0.18 (s, 3H), 0.92-0.95 (m, 3H), 0.96 (s, 9H),

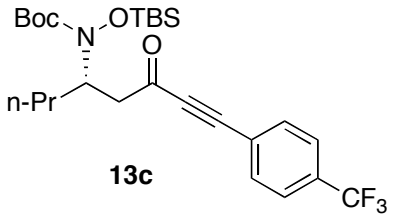
1.36-1.45 (m, 3H), 1.48 (s, 9H), 1.78 (m, 1H), 2.79 (dd, 1H, J_1 = 6.9 and J_2 = 16.3 Hz), 3.09 (dd, 1H, J_1 = 6.6 and J_2 = 16.3 Hz), 4.46 (m, 1H), 7.36-7.40 (m, 2H), 7.43-7.47 (m, 1H), 7.56-7.58 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.4, 13.9, 18.2, 19.7, 26.0, 28.2, 34.8, 48.5, 58.9, 81.4, 88.0, 90.8, 120.0, 128.6, 130.7, 133.0, 158.5, 185.5 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 468.2546, found *m/z* 468.2540.



13b

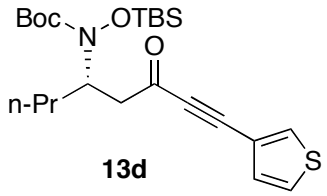
(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(8-(4-methoxyphenyl)-6-oxooct-7-yn-4-yl)carbamate (13b): Compound **14b** (0.240 g, 0.50 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (15 mL) and activated MnO_2 (1.54 g, 15.1 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (162 mg, 68%). IR (thin film) 2925, 2858, 2208, 1680, 1458, 1384, 1364, 1177, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.91-0.94 (m, 3H), 0.96 (s, 9H), 1.35-1.44 (m, 3H), 1.47 (s, 9H), 1.77 (m, 1H), 2.78 (dd, 1H, J_1 = 7.1 and J_2 = 16.2 Hz), 3.07 (dd, 1H, J_1 = 6.4 and J_2 = 16.2 Hz), 3.84 (s, 3H), 4.46 (m, 1H), 6.89 (d, 2H, J = 6.8 Hz), 7.52 (d, 2H, J = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 12.8, 17.2, 18.6, 25.1, 27.1, 33.7, 47.5, 54.4, 58.0, 80.3, 86.9, 91.0,

110.8, 113.3, 133.9, 157.4, 160.6, 184.4 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 498.2652, found *m/z* 498.2644.



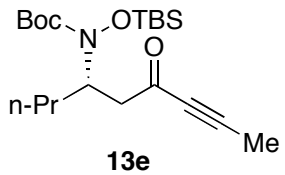
13c

(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(6-oxo-8-(4-(trifluoromethyl)phenyl)oct-7-yn-4-yl)carbamate (13c): Compound **14c** (0.151 g, 0.294 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (10 mL) and activated MnO_2 (0.901 g, 8.81 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (136 mg, 90%). IR (thin film) 2925, 2854, 2204, 1695, 1458, 1384, 1364, 1168, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 3H), 0.18 (s, 3H), 0.87-0.93 (m, 3H), 0.95 (s, 9H), 1.39-1.44 (m, 3H), 1.47 (s, 9H), 1.64 (br s, 1H), 1.77 (m, 1H), 2.78 (dd, 1H, J_1 = 6.5 and J_2 = 16.3 Hz), 3.11 (dd, 1H, J_1 = 7.0 and J_2 = 16.3 Hz), 4.46 (m, 1H), 7.62-7.68 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 12.8, 17.2, 18.6, 25.1, 27.2, 33.8, 47.4, 57.8, 80.5, 87.1, 88.2, 122.9, 124.5, 124.6, 131.9, 132.1, 157.5, 184.1 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 536.2420, found *m/z* 536.2411.



13d

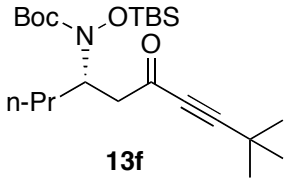
(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(6-oxo-8-(thiophen-3-yl)oct-7-yn-4-yl)carbamate (13d): Compound **14d** (0.161 g, 0.355 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (10 mL) and activated MnO_2 (1.09 g, 10.7 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (160 mg, 100%). IR (thin film) 2960, 2932, 2205, 1689, 1456, 1383, 1369, 1158, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.91-0.94 (m, 3H), 0.95 (s, 9H), 1.35-1.44 (m, 3H), 1.47 (s, 9H), 1.76 (m, 1H), 2.77 (dd, 1H, J_1 = 7.2 and J_2 = 16.7 Hz), 3.07 (dd, 1H, J_1 = 6.5 and J_2 = 16.4 Hz), 4.44 (m, 1H), 7.21 (d, 1H, J = 4.9 Hz) 7.32 (s, 1H), 7.74 (d, 1H, J = 2.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 12.8, 17.2, 18.6, 25.1, 27.2, 33.7, 47.4, 57.9, 80.4, 85.2, 87.2, 118.3, 125.1, 129.2, 132.8, 157.4, 184.4 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 474.2110, found *m/z* 474.2101.



13e

(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(6-oxonon-7-yn-4-yl)carbamate (13e):

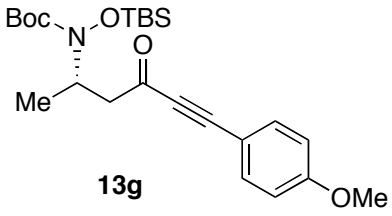
Compound **14e** (0.317 g, 0.821 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (23 mL) and activated MnO_2 (2.52 g, 24.6 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (242 mg, 77%). IR (thin film) 2961, 2933, 2216, 1670, 1384, 1364, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.87-0.91 (m, 3H), 0.93 (s, 9H), 1.31-1.41 (m, 3H), 1.46 (s, 9H), 1.72 (m, 1H), 1.99 (s, 3H), 2.62 (dd, 1H, J_1 = 7.0 and J_2 = 16.2 Hz), 2.92 (dd, 1H, J_1 = 6.4 and J_2 = 16.2 Hz), 4.36 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.4, 13.8, 18.0, 19.6, 26.0, 28.2, 34.7, 48.5, 58.8, 80.4, 81.3, 90.2, 158.4, 185.6 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 406.2390, found *m/z* 406.2383.



13f

(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(9,9-dimethyl-6-oxodec-7-yn-4-yl)carbamate (13f): Compound **14f** (0.277 g, 0.648 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (15 mL) and activated MnO_2 (1.99 g, 19.4 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow

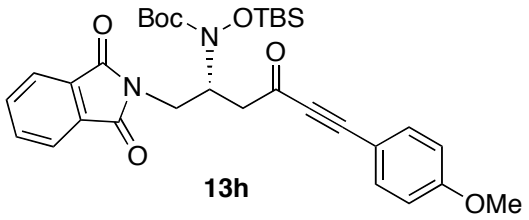
oil (249 mg, 90%). IR (thin film) 2964, 2934, 2874, 2220, 1698, 1459, 1383, 1369, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.16 (s, 3H), 0.89-0.94 (m, 3H), 0.95 (s, 9H), 1.27 (s, 9H), 1.30-1.44 (m, 3H), 1.48 (s, 9H), 1.75 (m, 1H), 2.66 (dd, 1H, J_1 = 7.2 and J_2 = 16.4 Hz), 2.95 (dd, 1H, J_1 = 6.2 and J_2 = 16.4 Hz), 4.35 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5, 13.8, 18.2, 19.6, 26.0, 27.7, 28.2, 30.0, 34.6, 48.6, 58.8, 79.5, 81.3, 101.5, 158.4, 185.7 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 448.2859, found *m/z* 448.2852.



13g

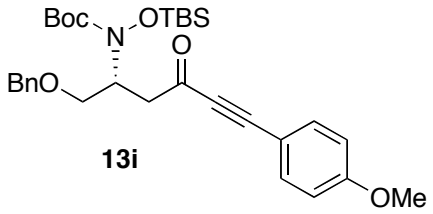
(*S*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(6-(4-methoxyphenyl)-4-oxohex-5-yn-2-yl)carbamate (13g): Compound **14g** (0.400 g, 0.889 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (25 mL) and activated MnO_2 (2.73 g, 26.7 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (213 mg, 54%). IR (thin film) 2928, 2208, 1682, 1384, 1364, 1177, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.96 (s, 9H), 1.28 (d, 3H J = 6.7 Hz), 1.48 (s, 9H), 2.88 (dd, 1H, J_1 = 8.5 and J_2 = 16.1 Hz), 3.04 (dd, 1H, J_1 = 5.1 and J_2 = 16.1 Hz), 3.83 (s, 3H), 4.46 (m, 1H), 6.88 (d, 2H, J = 8.8 Hz), 7.52 (d, 2H, J = 8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5, 16.5, 17.1, 25.1, 27.1, 48.4, 54.4,

58.0, 80.6, 86.9, 91.2, 110.7, 113.3, 134.2, 157.5, 160.7, 184.3 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 470.2339, found *m/z* 470.2333.



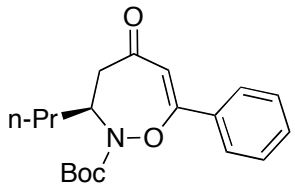
13h

(*R*)-*tert*-Butyl *tert*-Butyldimethylsilyloxy(1-(1,3-dioxoisoindolin-2-yl)-6-(4-methoxyphenyl)-4-oxohex-5-yn-2-yl)carbamate (13h): Compound **14h** (40. mg, 0.067 mmol, 1.0 equiv) was dissolved in 1,2-dichloroethane (10 mL) and activated MnO_2 (0.206 g, 2.02 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (40 mg, 100%). IR (thin film) 2900, 2206, 1686, 1450, 1384, 1364, 1177, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.19 (s, 3H), 0.88 (s, 9H), 1.46 (s, 9H), 2.97 (dd, 1H, J_1 = 6.5 and J_2 = 16.8 Hz), 3.25 (dd, 1H, J_1 = 6.8 and J_2 = 16.8 Hz), 3.85 (s, 3H), 3.90 (dd, 1H, J_1 = 6.8 and J_2 = 13.6 Hz), 4.14 (dd, 1H, J_1 = 7.2 and J_2 = 13.6 Hz), 4.79 (m, 1H), 6.89 (d, 2H, J = 8.8 Hz), 7.52 (d, 2H, J = 8.8 Hz), 7.68 (m, 2H), 7.81 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.8, 17.0, 24.9, 27.1, 38.0, 45.4, 54.4, 56.7, 81.0, 86.6, 91.8, 110.6, 113.3, 122.2, 131.1, 132.8, 134.2, 156.6, 160.7, 166.9, 183.0 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 615.2502, found *m/z* 615.2493.



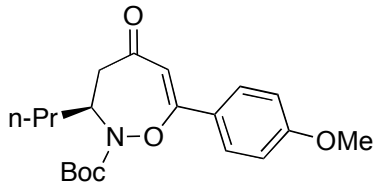
13i

(*R*)-*tert*-Butyl 1-(Benzyloxy)-6-(4-methoxyphenyl)-4-oxohex-5-yn-2-yl(*tert*-butyldimethylsilyloxy)carbamate (13i): Compound **14i** (0.240 g, 0.432 mmol, 1.00 equiv) was dissolved in 1,2-dichloroethane (15 mL) and activated MnO_2 (1.29 g, 12.6 mmol, 30.0 equiv) was added. The reaction mixture was refluxed overnight. After completion as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solution was concentrated *in vacuo* to give the title compound as a crude pale yellow oil (210 mg, 88%). IR (thin film) 2967, 2900, 2833, 2203, 1685, 1384, 1364, 1178, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.88 (s, 9H), 1.38 (s, 9H), 2.76 (dd, 1H, J_1 = 6.9 and J_2 = 16.3 Hz), 2.95 (dd, 1H, J_1 = 6.7 and J_2 = 16.3 Hz), 3.44 (dd, 1H, J_1 = 6.5 and J_2 = 9.7 Hz), 3.67 (dd, 1H, J_1 = 7.4 and J_2 = 9.7 Hz), 3.75 (s, 3H), 4.46 (s, 2H), 4.74 (m, 1H), 6.80 (d, 2H, J = 8.8 Hz), 7.17-7.27 (m, 5H), 7.44 (d, 2H, J = 8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5, 17.1, 25.2, 27.2, 44.4, 54.4, 57.5, 68.3, 71.9, 80.7, 86.8, 91.4, 110.7, 113.3, 126.5, 126.6, 127.3, 133.4, 137.2, 157.6, 160.6, 183.7 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 576.2757, found *m/z* 576.2751.



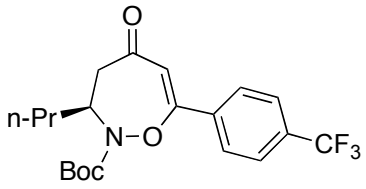
20a

(*S*)-*tert*-Butyl 5-Oxo-7-phenyl-3-propyl-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20a): Compound **13a** (0.304 g, 0.682 mmol, 1.00 equiv) was dissolved in THF (24 mL). Tetrabutylammonium fluoride (1.71 mmol, 1.00 M in tetrahydrofuran, 2.50 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (25% Et_2O/hexane) provided the title compound as yellow oil (173 mg, 77%). IR (thin film) 3402, 3069, 3026, 2925, 1710, 1664, 1619, 1493, 1452, 1384, 1367, 1158, 759, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.3 Hz), 1.40 (m, 2H), 1.49 (s, 9H), 1.69 (m, 1H), 1.83 (m, 1H), 2.88-2.92 (m, 2H), 4.59 (m, 1H), 5.89 (s, 1H), 7.40-7.50 (m, 3H), 7.91 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.0, 28.1, 35.3, 47.5, 58.4, 83.2, 108.3, 128.1, 128.7, 129.1, 132.0, 153.3, 173.7, 198.1 ppm; HRMS calculated for ($C_{19}H_{25}NO_4$) requires *m/z* [M+Na] 354.1682, found *m/z* 354.1680. $[\alpha]^{25}_D$ = -2.40 (c = 0.500, $CHCl_3$).



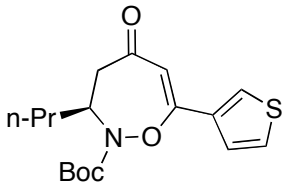
20b

(*S*)-*tert*-Butyl 7-(4-Methoxyphenyl)-5-oxo-3-propyl-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20b): Compound **13b** (0.162 g, 0.340 mmol, 1.00 equiv) was dissolved in THF (12 mL). Tetrabutylammonium fluoride (0.851 mmol, 1.00 M in tetrahydrofuran, 2.50 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as yellow oil (112 mg, 91%). IR (thin film) 3400, 2961, 2933, 1709, 1659, 1604, 1510, 1458, 1384, 1369, 1332, 1256, 1177, 841 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.36 (m, 2H), 1.46 (s, 9H), 1.67 (m, 1H), 1.76 (m, 1H), 2.81-2.91 (m, 2H), 3.82 (s, 3H), 4.54 (m, 1H), 5.76 (s, 1H), 6.90 (d, 2H, J = 9 Hz), 7.84 (d, 2H, J = 8.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.9, 28.0, 35.4, 47.1, 55.5, 58.4, 82.9, 106.8, 114.0, 124.3, 129.8, 153.2, 162.6, 174.0, 197.9 ppm; HRMS calculated for ($C_{20}H_{27}NO_5$) requires *m/z* [M+Na] 384.1787, found *m/z* 384.1782. $[\alpha]^{25}_D$ = -6.20 (c = 0.500, $CHCl_3$).



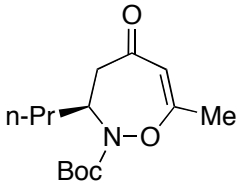
20c

(*S*)-*tert*-Butyl 5-Oxo-3-propyl-7-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20c): Compound **13c** (0.108 g, 0.210 mmol, 1.00 equiv) was dissolved in THF (7 mL). Tetrabutylammonium fluoride (0.63 mmol, 1.0 M in tetrahydrofuran, 3.0 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as yellow oil (19.5 mg, 23%). IR (thin film) 3400, 2925, 2854, 1737, 1683, 1650, 1459, 1384, 1364, 1324, 1246, 1169, 875 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.40 (m, 2H), 1.50 (s, 9H), 1.62-1.74 (m, 1H), 1.78-1.87 (m, 1H), 2.92 (m, 2H), 4.59 (m, 1H), 5.95 (s, 1H), 7.68 (d, 2H, J = 8.3 Hz), 8.04 (d, 2H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.9, 28.1, 35.0, 47.4, 58.5, 83.4, 109.9, 122.4, 125.5, 128.1, 132.9, 135.4, 153.2, 171.7, 197.7 ppm; HRMS calculated for ($C_{20}H_{24}F_3NO_4$) requires *m/z* [M+Na] 422.1555, found *m/z* 422.1553. $[\alpha]^{25}_D$ = +3.00 (c = 0.500, $CHCl_3$).



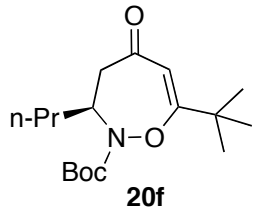
20d

(*S*)-*tert*-Butyl 5-Oxo-3-propyl-7-(thiophen-3-yl)-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20d): Compound **13d** (0.095 g, 0.209 mmol, 1.00 equiv) was dissolved in THF (7 mL). Tetrabutylammonium fluoride (0.628 mmol, 1.00 M in tetrahydrofuran, 3.00 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as yellow oil (45.4 mg, 64%). IR (thin film) 3401, 2961, 2931, 1709, 1662, 1618, 1457, 1383, 1369, 1254, 1158, 1088, 849 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.3 Hz), 1.38-1.43 (m, 2H), 1.47 (s, 9H), 1.62-1.72 (m, 1H), 1.77-1.86 (m, 1H), 2.91 (m, 2H), 4.54 (m, 1H), 5.81 (s, 1H), 7.31-7.36 (m, 2H), 8.07 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.9, 28.1, 35.4, 47.3, 58.0, 82.9, 107.9, 125.8, 126.8, 126.9, 134.3, 153.1, 168.9, 197.9 ppm; HRMS calculated for ($C_{17}H_{23}NO_4S$) requires *m/z* [M+Na] 360.1246, found *m/z* 360.1237. $[\alpha]^{25}_D$ = -1.80 (c = 0.500, $CHCl_3$).



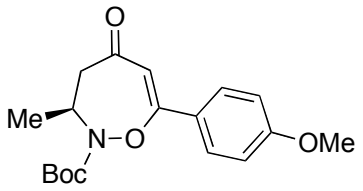
20e

(*S*)-*tert*-Butyl 7-Methyl-5-oxo-3-propyl-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20e): Compound **13e** (0.117 g, 0.305 mmol, 1.00 equiv) was dissolved in THF (11 mL). Tetrabutylammonium fluoride (0.763 mmol, 1.00 M in tetrahydrofuran, 2.50 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as yellow oil (60.1 mg, 73%). IR (thin film) 3400, 2962, 2933, 1710, 1667, 1384, 1365, 1254, 1142 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.3 Hz), 1.38 (m, 2H), 1.47 (s, 9H), 1.66-1.88 (m, 2H), 2.11 (s, 3H), 2.81 (m, 2H), 4.42 (m, 1H), 5.31 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 19.9, 28.0, 35.1, 47.4, 56.7, 82.6, 110.2, 152.6, 173.9, 197.6 ppm; HRMS calculated for ($C_{14}H_{23}NO_4$) requires *m/z* [M+Na] 292.1525, found *m/z* 292.1512. $[\alpha]^{25}_D$ = +5.80 (c = 0.500, $CHCl_3$).



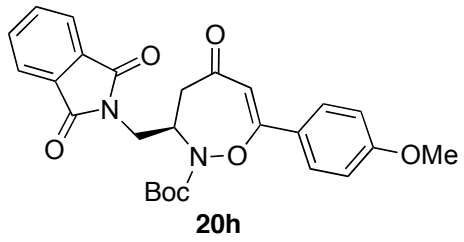
20f

(*S*)-*tert*-Butyl 7-*tert*-Butyl-5-oxo-3-propyl-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20f): Compound **13f** (0.138 g, 0.325 mmol, 1.00 equiv) was dissolved in THF (11 mL). Tetrabutylammonium fluoride (1.29 mmol, 1.00 M in tetrahydrofuran, 4.00 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (10% Et_2O/hexane) provided the title compound as yellow oil (52.4 mg, 52%). IR (thin film) 3402, 2964, 2934, 2874, 1739, 1710, 1628, 1459, 1383, 1369, 1318, 1255, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.3 Hz), 1.24 (s, 9H), 1.37 (m, 2H), 1.56-1.63 (m, 1H), 1.73-1.82 (m, 1H), 2.72 (dd, 1H, J_1 = 7.8 and J_2 = 14.9 Hz), 2.87 (dd, 1H, J_1 = 7.2 and J_2 = 11.5 Hz), 4.46 (m, 1H), 5.33 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 28.2, 34.4, 47.1, 57.1, 82.8, 105.5, 153.3, 181.9, 199.1 ppm; HRMS calculated for ($C_{17}H_{29}NO_4$) requires *m/z* [M+Na] 334.1995, found *m/z* 334.1988. $[\alpha]^{25}_D$ = +14.2 (*c* = 0.500, $CHCl_3$).



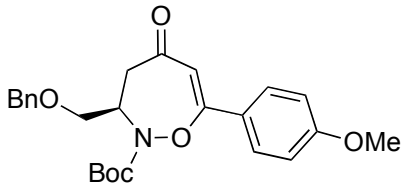
20g

(*S*)-*tert*-Butyl 7-(4-Methoxyphenyl)-3-methyl-5-oxo-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20g): Compound **13g** (0.213 g, 0.476 mmol, 1.00 equiv) was dissolved in THF (15 mL). Tetrabutylammonium fluoride (1.43 mmol, 1.00 M in tetrahydrofuran, 3.00 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as yellow oil (70 mg, 44%). IR (thin film) 3401, 2928, 1711, 1658, 1604, 1452, 1384, 1364, 1257, 1177, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, 3H, J = 6.3 Hz), 1.52 (s, 9H), 2.79 (m, 1H), 2.87 (m, 1H), 3.86 (s, 3H), 4.63 (m, 1H), 5.82 (s, 1H), 6.93 (d, 2H, J = 9 Hz), 7.89 (d, 2H, J = 9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 28.9, 48.7, 55.4, 55.6, 83.1, 107.2, 114.3, 124.3, 129.8, 153.6, 162.6, 174.4, 197.8 ppm; HRMS calculated for ($C_{18}H_{23}NO_5$) requires *m/z* [M+Na] 356.1474, found *m/z* 356.1263. $[\alpha]^{25}_D$ = -7.00 (*c* = 0.500, $CHCl_3$).



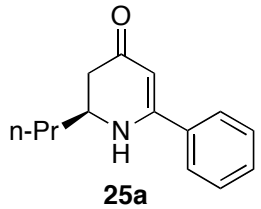
20h

(*R*)-*tert*-Butyl 3-((1,3-Dioxoisoindolin-2-yl)methyl)-7-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20h): Compound **13h** (39.9 mg, 0.0672 mmol, 1.00 equiv) was dissolved in THF (4 mL). Tetrabutylammonium fluoride (0.202 mmol, 1.00 M in tetrahydrofuran, 3.00 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (30% EtOAc/hexane) provided the title compound as yellow oil (13.7 mg, 43%). IR (thin film) 3400, 2900, 1718, 1667, 1603, 1450, 1384, 1364, 1256, 1177, 826 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.87 (m, 1H), 3.0 (m, 1H), 3.86 (s, 3H), 3.88 (m, 1H), 4.10 (m, 1H), 4.99 (m, 1H), 5.83 (s, 1H), 6.93 (d, 2H, *J* = 8.9 Hz), 7.72 (m, 2H), 7.87 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 39.1, 44.8, 55.4, 56.8, 83.4, 106.7, 114.1, 123.5, 123.9, 129.9, 132.1, 134.2, 152.5, 162.8, 167.9, 175.0, 196.2 ppm; HRMS calculated for ($C_{26}H_{26}N_2O_7$) requires *m/z* [M+Na] 501.1638, found *m/z* 501.1632. $[\alpha]^{25}_D$ = -80.6 (*c* = 0.500, $CHCl_3$).



20i

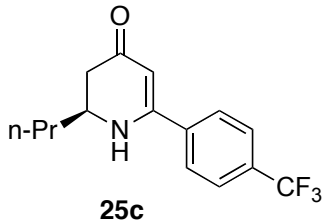
(*R*)-*tert*-Butyl 3-(Benzyloxymethyl)-7-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1,2-oxazepine-2(3*H*)-carboxylate (20i): Compound **13i** (0.210 g, 0.379 mmol, 1.00 equiv) was dissolved in THF (9 mL). Tetrabutylammonium fluoride (1.14 mmol, 1.00 M in tetrahydrofuran, 3.00 equiv) was added at room temperature to the above solution. The reaction mixture was allowed to stir for 1 min. After 1 min, when reaction was complete as indicated by TLC, the reaction mixture was quenched by silica gel, concentrated *in vacuo*. Purification by silica gel column chromatography (20% Et_2O/hexane) provided the title compound as yellow oil (80 mg, 48%). IR (thin film) 3400, 2967, 2900, 2833, 1750, 1733, 1667, 1604, 1384, 1364, 1257, 1178, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.86-2.99 (m, 2H), 3.60 (m, 1H), 3.76 (m, 1H), 3.85 (s, 3H), 4.56 (s, 2H), 4.84 (m, 1H), 5.81 (s, 1H), 6.93 (d, 2H, J = 8.9 Hz), 7.26 (m, 3H), 7.33 (m, 2H), 7.87 (d, 2H, J = 8.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 44.2, 55.4, 57.8, 69.6, 73.1, 83.1, 106.9, 114.1, 124.2, 127.6, 127.7, 128.4, 129.9, 137.8, 152.3, 162.7, 173.9, 175.0, 197.2 ppm; HRMS calculated for ($C_{25}H_{29}NO_6$) requires *m/z* [M+Na] 462.1893, found *m/z* 462.1886. $[\alpha]^{25}_D$ = -50.8 (c = 0.500, $CHCl_3$).



25a

(*S*)-6-Phenyl-2-propyl-2,3-dihydropyridin-4(1*H*)-one (25a): To an oven dried 10 mL round-bottom flask charged with **20a** (50.0 mg, 0.151 mmol, 1.00 equiv) in degassed MeOH (1 mL) was added SmI_2 (4.53 mL, 0.453 mmol, 0.100 M in tetrahydrofuran, 3.00 equiv) under an argon atmosphere. The deep-blue solution was allowed to stir at room temperature until the reaction turned pale yellow (2 min) or deemed complete by TLC. The solvent was removed *in vacuo* then the residue re-suspended in dichloromethane (20 mL). The organic layer was washed successively aqueous 1 M $NaHSO_4$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude compound. (33 mg, 66%). To a solution of this crude compound (33.0 mg, 0.099 mmol) in Dichloromethane (1 mL) was added Trifluoroacetic Acid (TFA) (54 μL). The reaction mixture was stirred until TLC showed the reaction was complete (~24 h). The reaction mixture was then diluted with DCM (20 mL), washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford pure title compound (13.7 mg, 60%). IR (thin film) 3403, 2900, 2858, 1617, 1531, 1384, 1325, 759, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.3 Hz), 1.44 (m, 2H), 1.73 (m, 2H), 2.39 (m, 1H), 2.49 (m, 1H), 3.80 (m, 1H), 4.89 (br s, 1H), 5.39 (s, 1H), 7.41-7.44 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.8, 36.5, 41.5, 53.3, 98.2, 126.1, 129.1, 130.9, 135.9, 161.2, 193.3 ppm; HRMS calculated for ($C_{14}H_{17}NO$) requires *m/z* [M+Na] 238.1208, found *m/z*

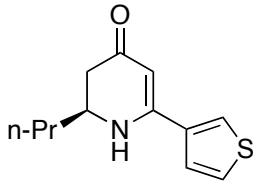
238.1198. $[\alpha]^{25}_{D}$ = -61.4 (*c* = 0.500, $CHCl_3$).



25c

(*S*)-2-Propyl-6-(4-(trifluoromethyl)phenyl)-2,3-dihydropyridin-4(1*H*)-one (25c): To an oven dried 10 mL round-bottom flask charged with **20c** (19.5 mg, 0.0488 mmol, 1.00 equiv) in degassed MeOH (1 mL) was added SmI_2 (1.47 mL, 0.147 mmol, 0.100 M in tetrahydrofuran, 3.00 equiv) under an argon atmosphere. The deep-blue solution was allowed to stir at room temperature until the reaction turned pale yellow (2 min) or deemed complete by TLC. The solvent was removed *in vacuo* then the residue re-suspended in dichloromethane (20 mL). The organic layer was washed successively aqueous 1 M $NaHSO_4$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude title compound. (17.8 mg, 91%). To a solution of this crude compound (17.8 mg, 0.0443 mmol) in Dichloromethane (1 mL) was added Trifluoroacetic Acid (TFA) (24.5 μL). The reaction mixture was stirred until TLC showed the reaction was complete (~24 h). The reaction mixture was then diluted with DCM (20 mL), washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford pure title compound (9.8 mg, 78%). IR (thin film) 3401, 2900, 1625, 1533, 1384, 1325, 827 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J* = 7.3 Hz), 1.44 (m, 2H), 1.70 (m, 2H), 2.39 (m, 1H),

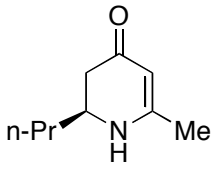
2.53 (m, 1H), 3.81 (m, 1H), 4.88 (br s, 1H), 5.37 (s, 1H), 7.63 (d, 2H, J = 8.2 Hz), 7.70 (d, 2H, J = 8.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.8, 36.5, 41.4, 53.4, 99.7, 122.6, 126.0, 126.6, 133.0, 139.4, 159.6, 193.3 ppm; HRMS calculated for ($C_{15}H_{16}F_3NO$) requires *m/z* [M+Na] 306.1082, found *m/z* 306.1078. $[\alpha]^{25}_D$ = -21.4 (*c* = 0.500, $CHCl_3$).



25d

(*S*)-2-Propyl-6-(thiophen-3-yl)-2,3-dihydropyridin-4(1*H*)-one (25d): To an oven dried 10 mL round-bottom flask charged with **20d** (45.4 mg, 0.135 mmol, 1.00 equiv) in degassed MeOH (1 mL) was added SmI_2 (4.04 mL, 0.404 mmol, 0.100 M in tetrahydrofuran, 3.00 equiv) under an argon atmosphere. The deep-blue solution was allowed to stir at room temperature until the reaction turned pale yellow (2 min) or deemed complete by TLC. The solvent was removed *in vacuo* then the residue re-suspended in dichloromethane (20 mL). The organic layer was washed successively aqueous 1 M $NaHSO_4$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude title compound. (34 mg, 75%). To a solution of this crude compound (34 mg, 0.10 mmol) in Dichloromethane (1 mL) was added Trifluoroacetic Acid (TFA) (55.3 μL). The reaction mixture was stirred until TLC showed the reaction was complete (~24 h). The reaction mixture was then diluted with DCM (20 mL), washed

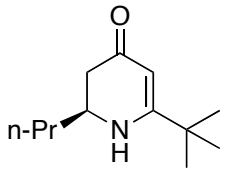
with sat. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford pure title compound (19.6 mg, 88%). IR (thin film) 3271, 2925, 1605, 1573, 1526, 1384, 1261, 787 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, 3H, *J* = 7.3 Hz), 1.44 (m, 2H), 1.69 (m, 2H), 2.36 (m, 1H), 2.49 (m, 1H), 3.78 (m, 1H), 5.03 (br s, 1H), 5.42 (s, 1H), 7.25 (m, 1H), 7.39 (m, 1H), 7.60 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.8, 36.5, 41.6, 53.1, 98.3, 124.5, 125.4, 127.2, 137.2, 155.7, 193.4 ppm; HRMS calculated for ($C_{12}H_{15}NOS$) requires *m/z* [M+Na] 244.0772, found *m/z* 244.0764. $[\alpha]^{25}_D$ = -128.2 (*c* = 0.5000, $CHCl_3$).



25e

(*S*)-6-Methyl-2-propyl-2,3-dihydropyridin-4(1*H*)-one (25e): To an oven dried 10 mL round-bottom flask charged with **20e** (30.0 mg, 0.111 mmol, 1.00 equiv) in degassed MeOH (1 mL) was added SmI_2 (3.34 mL, 0.334 mmol, 0.100 M in tetrahydrofuran, 3.00 equiv) under an argon atmosphere. The deep-blue solution was allowed to stir at room temperature until the reaction turned pale yellow (2 min) or deemed complete by TLC. The solvent was removed *in vacuo* then the residue re-suspended in dichloromethane (20 mL). The organic layer was washed successively aqueous 1 M $NaHSO_4$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude title compound. (20.8 mg, 69%). To a solution of this crude compound (20.8 mg, 0.0767 mmol) in Dichloromethane (1 mL) was added Trifluoroacetic Acid

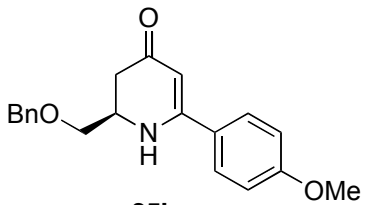
(TFA) (42.4 μL). The reaction mixture was stirred until TLC showed the reaction was complete (~24 h). The reaction mixture was then diluted with DCM (20 mL), washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford pure title compound (11 mg, 100%). IR (thin film) 3271, 2967, 2926, 1617, 1592, 1533, 1384 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.3 Hz), 1.37-1.43 (m, 2H), 1.57-1.65 (m, 2H), 1.96 (s, 3H), 2.21-2.29 (m, 1H), 2.36-2.41 (m, 1H), 3.62 (m, 1H), 4.56 (br s, 1H), 4.95 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.6, 21.3, 36.6, 41.2, 53.2, 99.5, 161.3, 192.8 ppm; HRMS calculated for ($C_9H_{15}NO$) requires *m/z* [M+Na] 176.1051, found *m/z* 176.1045. $[\alpha]^{25}_D$ = -15.8 (*c* = 0.500, $CHCl_3$).



25f

(*S*)-6-*tert*-Butyl-2-propyl-2,3-dihydropyridin-4(1*H*)-one (25f): To an oven dried 10 mL round-bottom flask charged with **20f** (52.4 mg, 0.168 mmol, 1.00 equiv) in degassed MeOH (1 mL) was added SmI_2 (5.05 mL, 0.505 mmol, 0.100 M in tetrahydrofuran, 3.00 equiv) under an argon atmosphere. The deep-blue solution was allowed to stir at room temperature until the reaction turned pale yellow (2 min) or deemed complete by TLC. The solvent was removed *in vacuo* then the residue re-suspended in dichloromethane (20 mL). The organic layer was washed successively aqueous 1 M $NaHSO_4$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to

give crude title compound. (52.1 mg, 99%). To a solution of this crude compound (52.0 mg, 0.166 mmol) in Dichloromethane (1 mL) was added Trifluoroacetic Acid (TFA) (91.7 μL). The reaction mixture was stirred until TLC showed the reaction was complete (~24 h). The reaction mixture was then diluted with DCM (20 mL), washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford pure title compound (32.4 mg, 100%). IR (thin film) 3301, 2959, 2925, 1605, 1513, 1465, 1384, 1364, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.18 (s, 9H), 1.43 (m, 2H), 1.63 (m, 2H), 2.23 (dd, 1H, J_1 = 12.6 and J_2 = 16.1 Hz), 2.40 (dd, 1H, J_1 = 4.9 and J_2 = 16.1 Hz), 3.59 (m, 1H), 4.76 (br s, 1H), 5.12 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.7, 28.6, 35.3, 36.3, 41.1, 53.1, 96.0, 172.6, 193.4 ppm; HRMS calculated for ($C_{12}H_{21}NO$) requires *m/z* [M+Na] 218.1521, found *m/z* 218.1518. $[\alpha]^{25}_D$ = -73.4 (*c* = 0.500, $CHCl_3$).



25i

(*R*)-2-(Benzyloxymethyl)-6-(4-methoxyphenyl)-2,3-dihydropyridin-4(1*H*)-one (25i): To an oven dried 10 mL round-bottom flask charged with **20i** (40.0 mg, 0.0910 mmol, 1.00 equiv) in degassed MeOH (1 mL) was added SmI_2 (2.73 mL, 0.273 mmol, 0.100 M in tetrahydrofuran, 3.00 equiv) under an argon atmosphere. The deep-blue solution was allowed to stir at room temperature until the reaction turned pale

yellow (2 min) or deemed complete by TLC. The solvent was removed *in vacuo* then the residue re-suspended in dichloromethane (20 mL). The organic layer was washed successively aqueous 1 M $NaHSO_4$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude compound. (30 mg, 75%). To a solution of this crude compound (30.0 mg, 0.0686 mmol) in Dichloromethane (1 mL) was added Trifluoroacetic Acid (TFA) (53.3 μL). The reaction mixture was stirred until TLC showed the reaction was complete (~24 h). The reaction mixture was then diluted with DCM (20 mL), washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford pure title compound (16.4 mg, 75%). IR (thin film) 3401, 2918, 1604, 1508, 1384, 1258, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (m, 2H), 3.63 (m, 2H), 3.85 (s, 3H), 3.99-4.07 (m, 1H), 4.59 (s, 2H), 5.37 (s, 1H), 5.47 (br s, 1H), 6.94 (d, 2H, J = 8.8Hz), 7.32-7.37 (m, 5H), 7.45 (d, 2H, J = 8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.7, 52.7, 55.5, 71.6, 73.4, 97.9, 114.4, 127.5 127.9, 128.1, 128.6, 137.4, 160.9, 161.8, 191.8 ppm; HRMS calculated for ($C_{20}H_{21}NO_3$) requires *m/z* [M+Na] 346.1419, found *m/z* 346.1418. $[\alpha]^{25}_D$ = -86.4 (c = 0.500, $CHCl_3$).

6. References

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